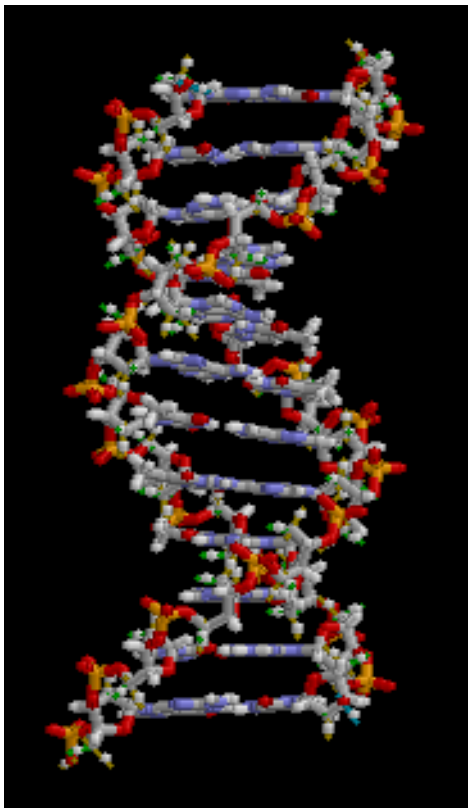
DNA Molecular Structure and Dynamics:

Biochemistry, Techniques and Molecular Modeling

DNA Biochemistry and Structure

DNA

Deoxyribonucleic acid (**DNA**) is a nucleic acid that contains the genetic instructions used in the development and functioning of all known living organisms and some viruses. The main role of DNA molecules is the long-term storage of information. DNA is often compared to a set of blueprints or a recipe, or a code, since it contains the instructions needed to construct other components of cells, such as proteins and RNA molecules. The DNA segments that carry this genetic information are called genes, but other DNA sequences have structural purposes, or are involved in regulating the use of this genetic information.



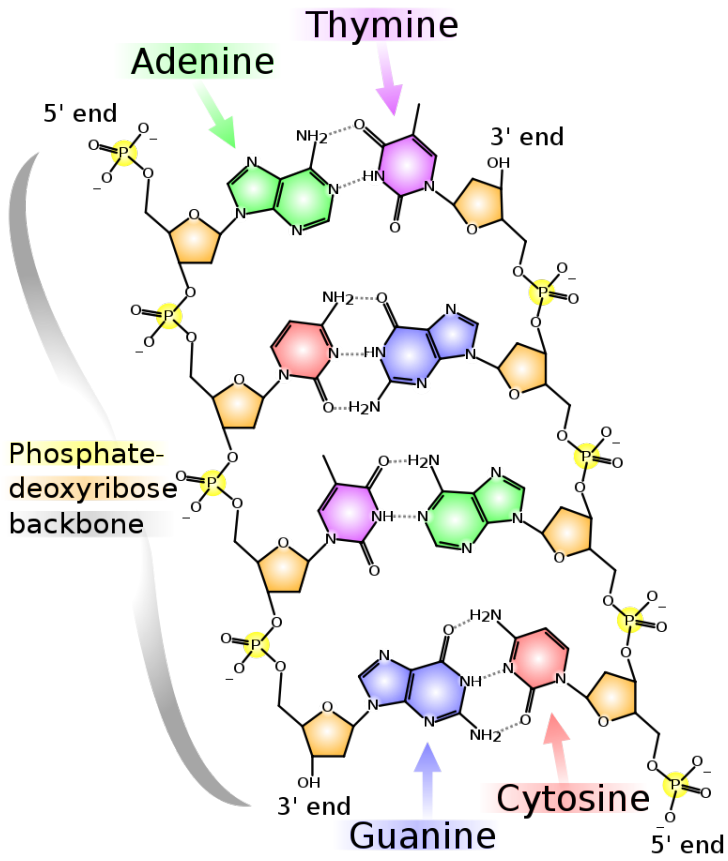
The structure of part of a DNA double helix

Chemically, DNA consists of two long polymers of simple units called nucleotides, with backbones made of sugars and phosphate groups joined by ester bonds. These two strands run in opposite directions to each other and are therefore anti-parallel. Attached to each sugar is one of four types of molecules called bases. It is the sequence of these four bases along the backbone that encodes information. This information is read using the genetic code, which specifies the sequence of the amino acids within proteins. The code is read by copying stretches of DNA into the related nucleic acid RNA, in a process called transcription.

Within cells, DNA is organized into structures called chromosomes. These chromosomes are duplicated before cells divide, in a process called DNA replication. Eukaryotic organisms (animals, plants, fungi, and protists) store most of their DNA inside the cell nucleus and some of their DNA in the mitochondria. Prokaryotes (bacteria and archaea) however, store their DNA in the cell's cytoplasm. Within the chromosomes, chromatin proteins such as histones compact and organize DNA. These compact structures guide the interactions between DNA and other proteins, helping control which parts of the DNA are transcribed.

Properties

DNA is a long polymer made from repeating units called nucleotides.[1] [2] [3] The DNA chain is 22 to 26 Ångströms wide (2.2 to 2.6 nanometres), and one nucleotide unit is 3.3 Å (0.33 nm) long.[4] Although each individual repeating unit is very small, DNA polymers can be very large molecules containing millions of nucleotides. For instance, the largest human chromosome, chromosome number 1, is approximately 220 million base pairs long.[5]



The chemical structure of DNA. Hydrogen bonds are shown as dotted lines.

In living organisms, DNA does not usually exist as a single molecule, but instead as a pair of molecules that are held tightly together.[6] [7] These two long strands entwine like vines, in the shape of a double helix. The nucleotide repeats contain both the segment of the backbone of the molecule, which holds the chain together, and a base, which interacts with the other DNA strand in the helix. In general, a base linked to a sugar is called a nucleoside and a base linked to a sugar and one or more phosphate groups is called a nucleotide. If multiple nucleotides are linked together, as in DNA, this polymer is called a polynucleotide.[8]

The backbone of the DNA strand is made from alternating phosphate and sugar residues.[9] The sugar in DNA is 2-deoxyribose, which is a pentose (five-carbon) sugar. The sugars are joined together by phosphate groups that form phosphodiester bonds between the third and fifth carbon atoms of adjacent sugar rings. These asymmetric bonds mean a strand of DNA has a direction. In a double helix the direction of the nucleotides in one strand is opposite to their direction in the other strand. This arrangement of DNA strands is called antiparallel. The asymmetric ends of DNA strands are referred to as the 5′ (*five prime*) and 3′ (*three prime*) ends, with the 5' end being that with a terminal phosphate group and the 3' end that with a terminal hydroxyl group. One of the major differences between DNA and RNA is the sugar, with 2-deoxyribose being replaced by the alternative pentose sugar ribose in RNA.[7]

The DNA double helix is stabilized by hydrogen bonds between the bases attached to the two strands. The four bases found in DNA are adenine (abbreviated A), cytosine (C), guanine (G) and thymine (T). These four bases are attached to the sugar/phosphate to form the complete nucleotide, as shown for adenosine monophosphate.

These bases are classified into two types; adenine and guanine are fused five- and six-membered heterocyclic compounds called purines, while cytosine and thymine are six-membered rings called pyrimidines.[7] A fifth pyrimidine base, called uracil (U), usually takes the place of thymine in RNA and differs from thymine by lacking a methyl group on its ring. Uracil is not usually found in DNA, occurring only as a breakdown product of cytosine.

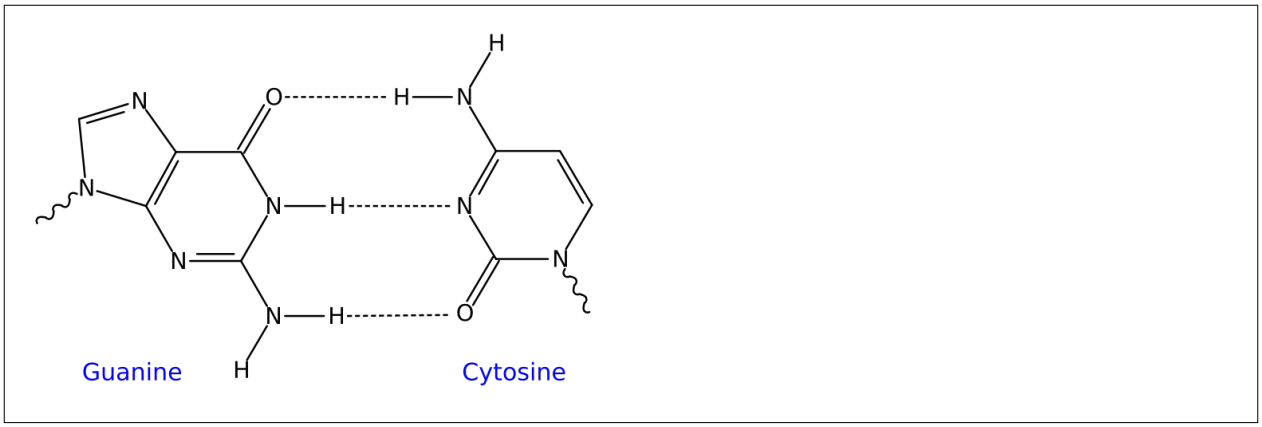
Grooves

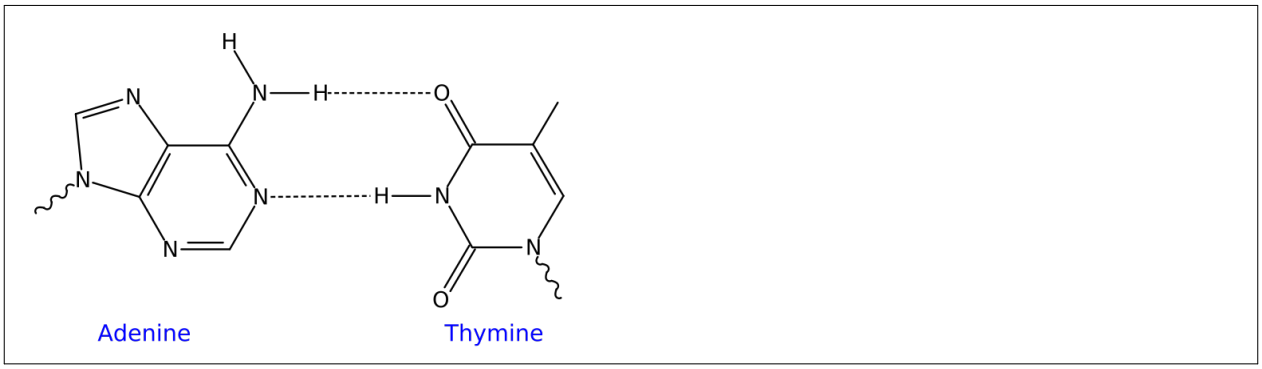
Twin helical strands form the DNA backbone. Another double helix may be found by tracing the spaces, or grooves, between the strands. These voids are adjacent to the base pairs and may provide a binding site. As the strands are not directly opposite each other, the grooves are unequally sized. One groove, the major groove, is 22 Å wide and the other, the minor groove, is 12 Å wide.[11] The narrowness of the minor groove means that the edges of the bases are more accessible in the major groove. As a result, proteins like transcription factors that can bind to specific sequences in double-stranded DNA usually make contacts to the sides of the bases exposed in the major groove.[12] This situation varies in unusual conformations of DNA within the cell *(see below)*, but the major and minor grooves are always named to reflect the differences in size that would be seen if the DNA is twisted back into the ordinary B form.

Structure of a section of DNA. The bases lie horizontally between the two spiraling strands.[10] Animated version at File:DNA orbit animated.gif - over 3 megabytes.

Base pairing

Each type of base on one strand forms a bond with just one type of base on the other strand. This is called complementary base pairing. Here, purines form hydrogen bonds to pyrimidines, with A bonding only to T, and C bonding only to G. This arrangement of two nucleotides binding together across the double helix is called a base pair. As hydrogen bonds are not covalent, they can be broken and rejoined relatively easily. The two strands of DNA in a double helix can therefore be pulled apart like a zipper, either by a mechanical force or high temperature.[13] As a result of this complementarity, all the information in the double-stranded sequence of a DNA helix is duplicated on each strand, which is vital in DNA replication. Indeed, this reversible and specific interaction between complementary base pairs is critical for all the functions of DNA in living organisms.[2]





Top, a **GC** base pair with three hydrogen bonds. Bottom, an **AT** base pair with two hydrogen bonds. Non-covalent hydrogen bonds between the pairs are shown as dashed lines.

The two types of base pairs form different numbers of hydrogen bonds, AT forming two hydrogen bonds, and GC forming three hydrogen bonds (see figures, left). DNA with high GC-content is more stable than DNA with low GC-content, but contrary to popular belief, this is not due to the extra hydrogen bond of a GC basepair but rather the contribution of stacking interactions (hydrogen bonding merely provides specificity of the pairing, not stability).[14] As a result, it is both the percentage of GC base pairs and the overall length of a DNA double helix that determine the strength of the association between the two strands of DNA. Long DNA helices with a high GC content have stronger-interacting strands, while short helices with high AT content have weaker-interacting strands.[15] In biology, parts of the DNA double helix that need to separate easily, such as the TATAAT Pribnow box in some promoters, tend to have a high AT content, making the strands easier to pull apart.[16] In the laboratory, the strength of this interaction can be measured by finding the temperature required to break the hydrogen bonds, their melting temperature (also called T_m value). When all the base pairs in a DNA double helix melt, the strands separate and exist in solution as two entirely independent molecules. These single-stranded DNA molecules have no single common shape, but some conformations are more stable than others.[17]

Sense and antisense

A DNA sequence is called "sense" if its sequence is the same as that of a messenger RNA copy that is translated into protein.[18] The sequence on the opposite strand is called the "antisense" sequence. Both sense and antisense sequences can exist on different parts of the same strand of DNA (i.e. both strands contain both sense and antisense sequences). In both prokaryotes and eukaryotes, antisense RNA sequences are produced, but the functions of these RNAs are not entirely clear.[19] One proposal is that antisense RNAs are involved in regulating gene expression through RNA-RNA base pairing.[20]

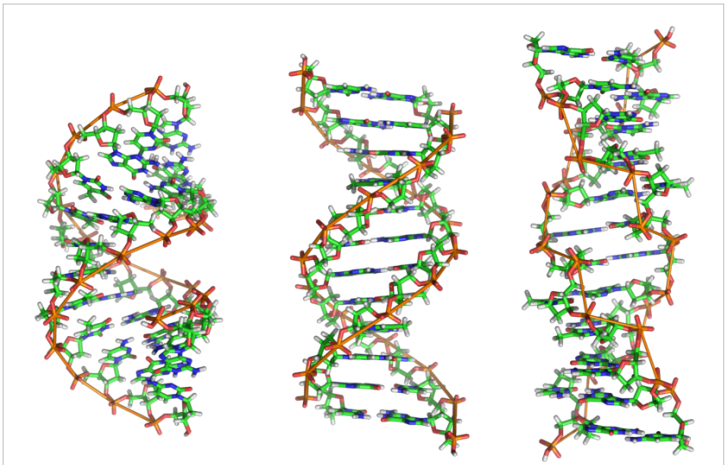
A few DNA sequences in prokaryotes and eukaryotes, and more in plasmids and viruses, blur the distinction between sense and antisense strands by having overlapping genes.[21] In these cases, some DNA sequences do double duty, encoding one protein when read along one strand, and a second protein when read in the opposite direction along the other strand. In bacteria, this overlap may be involved in the regulation of gene transcription,[22] while in viruses, overlapping genes increase the amount of information that can be encoded within the small viral genome.[23]

Supercoiling

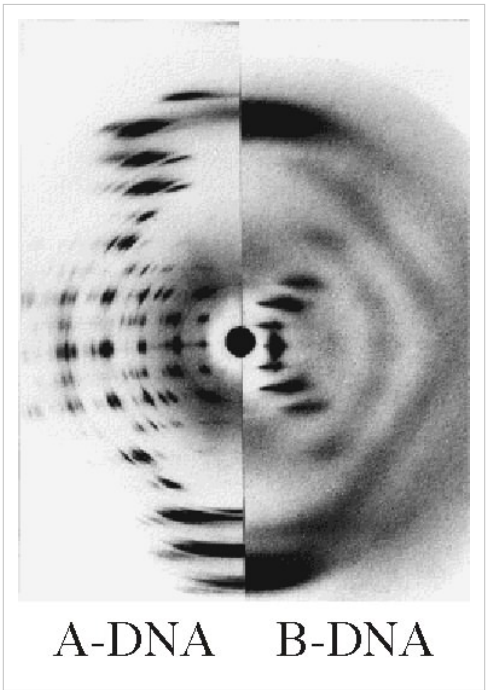
DNA can be twisted like a rope in a process called DNA supercoiling. With DNA in its "relaxed" state, a strand usually circles the axis of the double helix once every 10.4 base pairs, but if the DNA is twisted the strands become more tightly or more loosely wound.[24] If the DNA is twisted in the direction of the helix, this is positive supercoiling, and the bases are held more tightly together. If they are twisted in the opposite direction, this is negative supercoiling, and the bases come apart more easily. In nature, most DNA has slight negative supercoiling that is introduced by enzymes called topoisomerases.[25] These enzymes are also needed to relieve the twisting stresses introduced into DNA strands during processes such as transcription and DNA replication.[26]

Alternate DNA structures

DNA exists in many possible conformations that include A-DNA, B-DNA, and Z-DNA forms, although, only B-DNA and Z-DNA have been directly observed in functional organisms.[9] The conformation that DNA adopts depends on the hydration level, DNA sequence, the amount and direction of supercoiling, chemical modifications of the bases, the type and concentration of metal ions, as well as the presence of polyamines in solution.[27]



From left to right, the structures of A, B and Z DNA

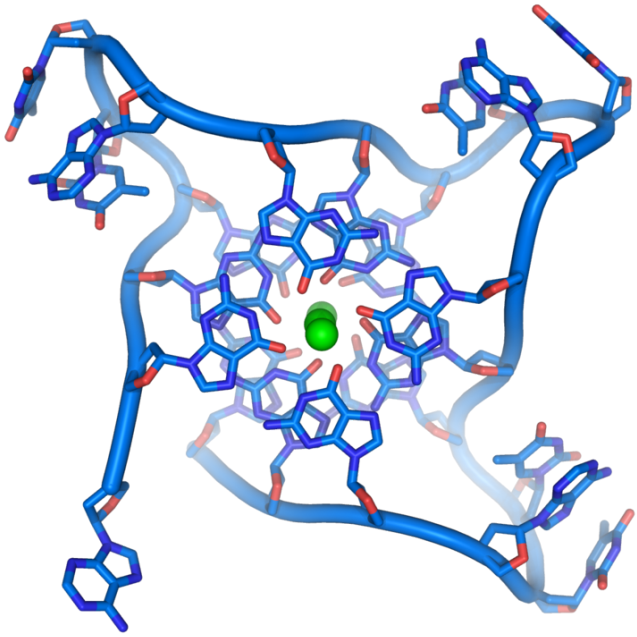


Gallery Fig.1. *X-ray diffraction patterns of A- and B- DNA: the much lower quality of the B-DNA form X-ray pattern—- with only a few 'Bragg diffraction' orders—- shows why its analysis requires the → paracrystal model approach.* (X-ray patterns are courtesy of Dr. H. R. Wilson, F.R.S).

The first published reports of A-DNA X-ray diffraction patterns— and also B-DNA used analyses based on Patterson transforms that provided only a limited amount of structural information for oriented fibers of DNA.[28] [29] An alternate analysis was then proposed by Wilkins *et al.*, in 1953, for the *in vivo* B-DNA X-ray diffraction/scattering patterns of highly hydrated DNA fibers in terms of squares of Bessel functions.[30] In the same journal, Watson and Crick presented their → molecular modeling analysis of the DNA X-ray diffraction patterns to suggest that the structure was a double-helix.[6]

Although the `B-DNA form' is most common under the conditions found in cells,[31] it is not a well-defined conformation but a family of related DNA conformations[32] that occur at the high hydration levels present in living cells. Their corresponding X-ray diffraction and scattering patterns are characteristic of molecular → paracrystals with a significant degree of disorder.[33] [34]

Compared to B-DNA, the A-DNA form is a wider right-handed spiral, with a shallow, wide minor groove and a narrower, deeper major groove. The A form occurs under non-physiological conditions in partially dehydrated samples of DNA, while in the cell it may be produced in hybrid pairings of DNA and RNA strands, as well as in enzyme-DNA complexes.[35] [36] Segments of DNA where the bases have been chemically modified by methylation may undergo a larger change in conformation and adopt the Z form. Here, the strands turn about the helical axis in a left-handed spiral, the opposite of the more common B form.[37] These unusual structures can be recognized by specific Z-DNA binding proteins and may be involved in the regulation of transcription.[38]



Structure of a DNA quadruplex formed by telomere repeats. The looped conformation of the DNA backbone is very different from the typical helical structure.[39]

Quadruplex structures

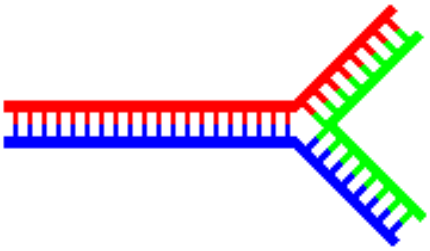
At the ends of the linear chromosomes are specialized regions of DNA called telomeres. The main function of these regions is to allow the cell to replicate chromosome ends using the enzyme telomerase, as the enzymes that normally replicate DNA cannot copy the extreme 3′ ends of chromosomes.[40] These specialized chromosome caps also help protect the DNA ends, and stop the DNA repair systems in the cell from treating them as damage to be corrected.[41] In human cells, telomeres are usually lengths of single-stranded DNA containing several thousand repeats of a simple TTAGGG sequence.[42]

These guanine-rich sequences may stabilize chromosome ends by forming structures of stacked sets of four-base units, rather than the usual base pairs found in other DNA molecules. Here, four guanine bases form a flat plate and these flat four-base units then stack on top of each other, to form a stable *G-quadruplex* structure.[43] These structures are stabilized by hydrogen bonding between the edges of the bases and chelation of a metal ion in the centre of each four-base unit.[44] Other structures can also be formed, with the central set of four bases coming from either a single strand folded around the bases, or several different parallel strands, each contributing one base to the central structure.

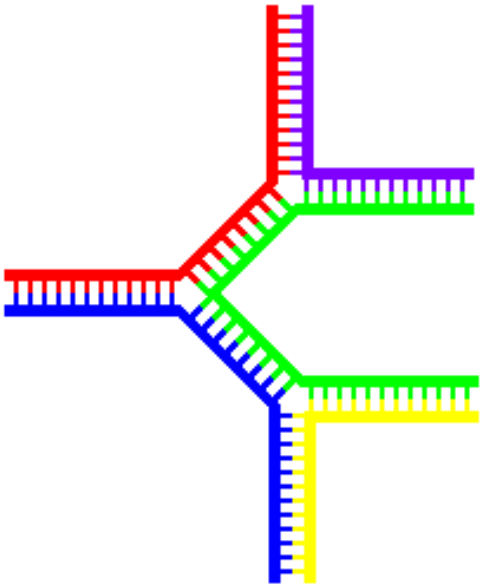
In addition to these stacked structures, telomeres also form large loop structures called telomere loops, or T-loops. Here, the single-stranded DNA curls around in a long circle stabilized by telomere-binding proteins.[45] At the very end of the T-loop, the single-stranded telomere DNA is held onto a region of double-stranded DNA by the telomere strand disrupting the double-helical DNA and base pairing to one of the two strands. This triple-stranded structure is called a displacement loop or D-loop.[43]

Branched DNA

In DNA fraying occurs when non-complementary regions exist at the end of an otherwise complementary double-strand of DNA. However, branched DNA can occur if a third strand of DNA is introduced and contains adjoining regions able to hybridize with the frayed regions of the pre-existing double-strand. Although the simplest example of branched DNA involves only three strands of DNA, complexes involving additional strands and multiple branches are also possible.[46]

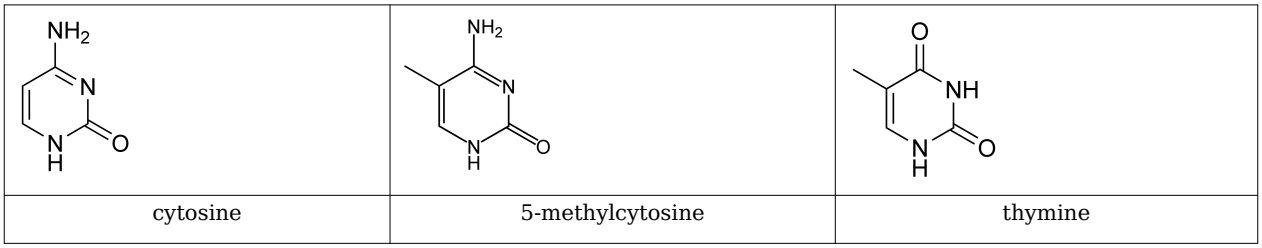


A DNA structure with a single branching point.



A DNA structure with multiple branches.

Chemical modifications



cytosine	5-methylcytosine	thymine

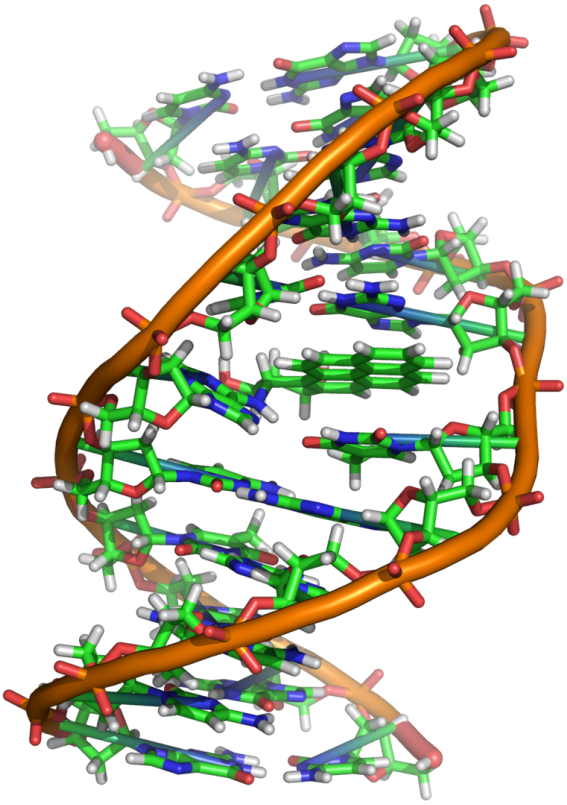
Structure of cytosine with and without the 5-methyl group. After deamination the 5-methylcytosine has the same structure as thymine

Base modifications

The expression of genes is influenced by how the DNA is packaged in chromosomes, in a structure called chromatin. Base modifications can be involved in packaging, with regions that have low or no gene expression usually containing high levels of methylation of cytosine bases. For example, cytosine methylation, produces 5-methylcytosine, which is important for X-chromosome inactivation.[47] The average level of methylation varies between organisms - the worm *Caenorhabditis elegans* lacks cytosine methylation, while vertebrates have higher levels, with up to 1% of their DNA containing 5-methylcytosine.[48] Despite the importance of 5-methylcytosine, it can deaminate to leave a thymine base, methylated cytosines are therefore particularly prone to mutations.[49] Other base modifications include adenine methylation in bacteria, the presence of 5-hydroxymethylcytosine in the brain,[50] and the glycosylation of uracil to produce the "J-base" in kinetoplastids.[51] [52]

Damage

DNA can be damaged by many different sorts of mutagens, which change the DNA sequence. Mutagens include oxidizing agents, alkylating agents and also high-energy electromagnetic radiation such as ultraviolet light and X-rays. The type of DNA damage produced depends on the type of mutagen. For example, UV light can damage DNA by producing thymine dimers, which are cross-links between pyrimidine bases.[54] On the other hand, oxidants such as free radicals or hydrogen peroxide produce multiple forms of damage, including base modifications, particularly of guanosine, and double-strand breaks.[55] A typical human cell contains about 150,000 bases that have suffered oxidative damage.[56] Of these oxidative lesions, the most dangerous are double-strand breaks, as these are difficult to repair and can produce point mutations, insertions and deletions from the DNA sequence, as well as chromosomal translocations.[57]



A covalent adduct between benzo[*a*]pyrene, the major mutagen in tobacco smoke, and DNA[53]

Many mutagens fit into the space between two adjacent base pairs, this is called *intercalating*. Most intercalators are aromatic and planar molecules, and include Ethidium bromide, daunomycin, and doxorubicin. In order for an intercalator to fit between base pairs, the bases must separate, distorting the DNA strands by unwinding of the double helix. This inhibits both transcription and DNA replication, causing toxicity and mutations. As a result, DNA intercalators are often carcinogens, and Benzo[*a*]pyrene diol epoxide, acridines, aflatoxin and ethidium bromide are well-known examples.[58] [59] [60] Nevertheless, due to their ability to inhibit DNA transcription and replication, other similar toxins are also used in chemotherapy to inhibit rapidly growing cancer cells.[61]

Biological functions

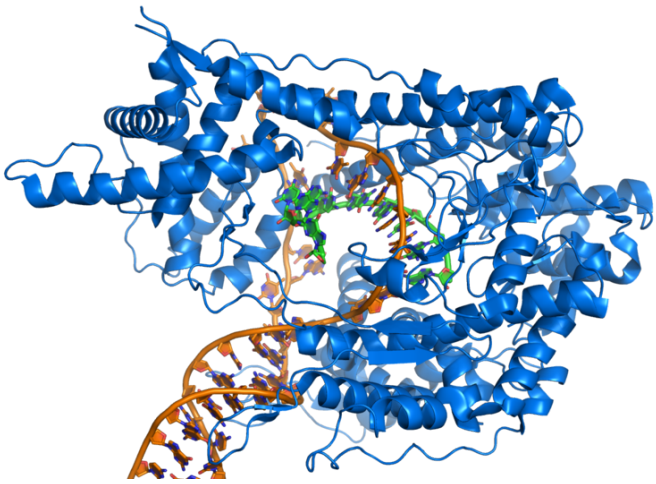
DNA usually occurs as linear chromosomes in eukaryotes, and circular chromosomes in prokaryotes. The set of chromosomes in a cell makes up its genome; the human genome has approximately 3 billion base pairs of DNA arranged into 46 chromosomes.[62] The information carried by DNA is held in the sequence of pieces of DNA called genes. Transmission of genetic information in genes is achieved via complementary base pairing. For example, in transcription, when a cell uses the information in a gene, the DNA sequence is copied into a complementary RNA sequence through the attraction between the DNA and the correct RNA nucleotides. Usually, this RNA copy is then used to make a matching protein sequence in a process called translation which depends on the same interaction between RNA nucleotides. Alternatively, a cell may simply copy its genetic

information in a process called DNA replication. The details of these functions are covered in other articles; here we focus on the interactions between DNA and other molecules that mediate the function of the genome.

Genes and genomes

Genomic DNA is located in the cell nucleus of eukaryotes, as well as small amounts in mitochondria and chloroplasts. In prokaryotes, the DNA is held within an irregularly shaped body in the cytoplasm called the nucleoid.[63] The genetic information in a genome is held within genes, and the complete set of this information in an organism is called its genotype. A gene is a unit of heredity and is a region of DNA that influences a particular characteristic in an organism. Genes contain an open reading frame that can be transcribed, as well as regulatory sequences such as promoters and enhancers, which control the transcription of the open reading frame.

In many species, only a small fraction of the total sequence of the genome encodes protein. For example, only about 1.5% of the human genome consists of protein-coding exons, with over 50% of human DNA consisting of non-coding repetitive sequences.[64] The reasons for the presence of so much non-coding DNA in eukaryotic genomes and the extraordinary differences in genome size, or *C-value*, among species represent a long-standing puzzle known as the "C-value enigma."[65] However, DNA sequences that do not code protein may still encode functional non-coding RNA molecules, which are involved in the regulation of gene expression.[66]



T7 RNA polymerase (blue) producing a mRNA (green) from a DNA template (orange).[67]

Some non-coding DNA sequences play structural roles in chromosomes. Telomeres and centromeres typically contain few genes, but are important for the function and stability of chromosomes.[41] [68] An abundant form of non-coding DNA in humans are pseudogenes, which are copies of genes that have been disabled by mutation.[69] These sequences are usually just molecular fossils, although they can occasionally serve as raw genetic material for the creation of new genes through the process of gene duplication and divergence.[70]

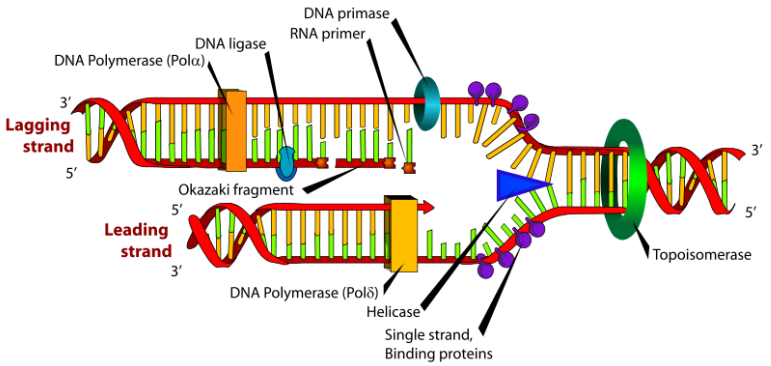
Transcription and translation

A gene is a sequence of DNA that contains genetic information and can influence the phenotype of an organism. Within a gene, the sequence of bases along a DNA strand defines a messenger RNA sequence, which then defines one or more protein sequences. The relationship between the nucleotide sequences of genes and the amino-acid sequences

of proteins is determined by the rules of translation, known collectively as the genetic code. The genetic code consists of three-letter 'words' called *codons* formed from a sequence of three nucleotides (e.g. ACT, CAG, TTT).

In transcription, the codons of a gene are copied into messenger RNA by RNA polymerase. This RNA copy is then decoded by a ribosome that reads the RNA sequence by base-pairing the messenger RNA to transfer RNA, which carries amino acids. Since there are 4 bases in 3-letter combinations, there are 64 possible codons (4^3 combinations). These encode the twenty standard amino acids, giving most amino acids more than one possible codon. There are also three 'stop' or 'nonsense' codons signifying the end of the coding region; these are the TAA, TGA and TAG codons.

Replication



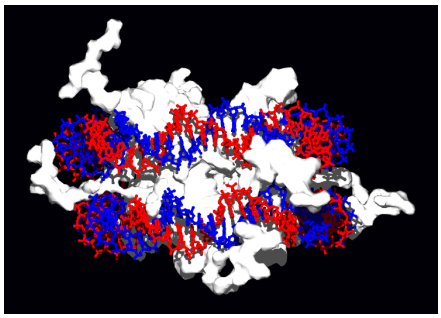
DNA replication. The double helix is unwound by a helicase and topoisomerase. Next, one DNA polymerase produces the leading strand copy. Another DNA polymerase binds to the lagging strand. This enzyme makes discontinuous segments (called Okazaki fragments) before DNA ligase joins them together.

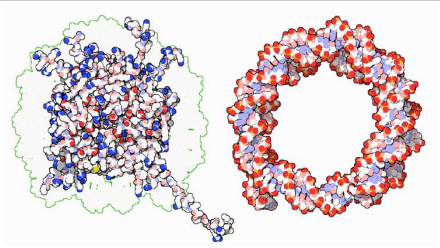
Cell division is essential for an organism to grow, but when a cell divides it must replicate the DNA in its genome so that the two daughter cells have the same genetic information as their parent. The double-stranded structure of DNA provides a simple mechanism for DNA replication. Here, the two strands are separated and then each strand's complementary DNA sequence is recreated by an enzyme called DNA polymerase. This enzyme makes the complementary strand by finding the correct base through complementary base pairing, and bonding it onto the original strand. As DNA polymerases can only extend a DNA strand in a 5′ to 3′ direction, different mechanisms are used to copy the antiparallel strands of the double helix.[71] In this way, the base on the old strand dictates which base appears on the new strand, and the cell ends up with a perfect copy of its DNA.

Interactions with proteins

All the functions of DNA depend on interactions with proteins. These protein interactions can be non-specific, or the protein can bind specifically to a single DNA sequence. Enzymes can also bind to DNA and of these, the polymerases that copy the DNA base sequence in transcription and DNA replication are particularly important.

DNA-binding proteins



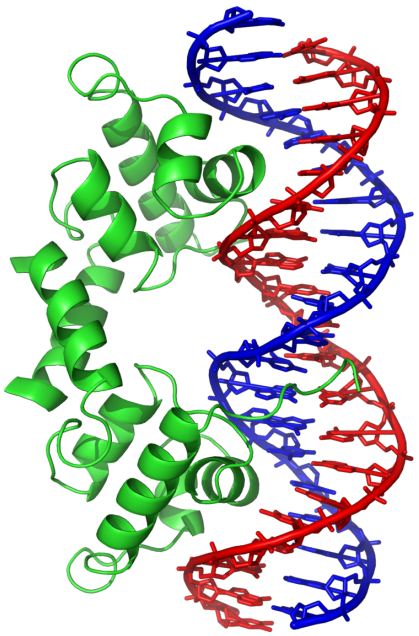


Interaction of DNA with histones (shown in white, top). These proteins' basic amino acids (below left, blue) bind to the acidic phosphate groups on DNA (below right, red).

Structural proteins that bind DNA are well-understood examples of non-specific DNA-protein interactions. Within chromosomes, DNA is held in complexes with structural proteins. These proteins organize the DNA into a compact structure called chromatin. In eukaryotes this structure involves DNA binding to a complex of small basic proteins called histones, while in prokaryotes multiple types of proteins are involved.[72] [73] The histones form a disk-shaped complex called a nucleosome, which contains two complete turns of double-stranded DNA wrapped around its surface. These non-specific interactions are formed through basic residues in the histones making ionic bonds to the acidic sugar-phosphate backbone of the DNA, and are therefore largely independent of the base sequence.[74] Chemical modifications of these basic amino acid residues include methylation, phosphorylation and acetylation.[75] These chemical changes alter the strength of the interaction between the DNA and the histones, making the DNA more or less accessible to transcription factors and changing the rate of transcription.[76] Other non-specific DNA-binding proteins in chromatin include the high-mobility group proteins, which bind to bent or distorted DNA.[77] These proteins are important in bending arrays of nucleosomes and arranging them into the larger structures that make up chromosomes.[78]

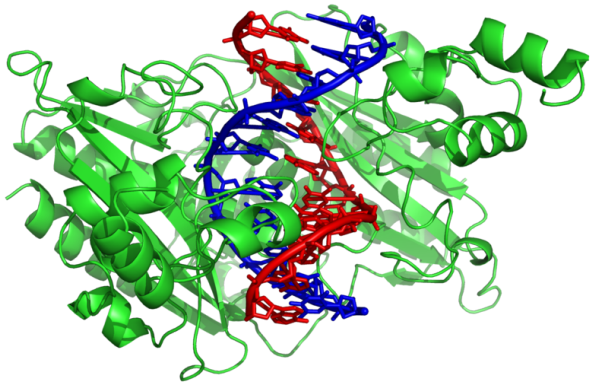
A distinct group of DNA-binding proteins are the DNA-binding proteins that specifically bind single-stranded DNA. In humans, replication protein A is the best-understood member of this family and is used in processes where the double helix is separated, including DNA replication, recombination and DNA repair.[79] These binding proteins seem to stabilize single-stranded DNA and protect it from forming stem-loops or being degraded by nucleases.

In contrast, other proteins have evolved to bind to particular DNA sequences. The most intensively studied of these are the various transcription factors, which are proteins that regulate transcription. Each transcription factor binds to one particular set of DNA sequences and activates or inhibits the transcription of genes that have these sequences close to their promoters. The transcription factors do this in two ways. Firstly, they can bind the RNA polymerase responsible for transcription, either directly or through other mediator proteins; this locates the polymerase at the promoter and allows it to begin transcription.[81] Alternatively, transcription factors can bind enzymes that modify the histones at the promoter; this will change the accessibility of the DNA template to the polymerase.[82]



The lambda repressor helix-turn-helix transcription factor bound to its DNA target[80]

As these DNA targets can occur throughout an organism's genome, changes in the activity of one type of transcription factor can affect thousands of genes.[83] Consequently, these proteins are often the targets of the signal transduction processes that control responses to environmental changes or cellular differentiation and development. The specificity of these transcription factors' interactions with DNA come from the proteins making multiple contacts to the edges of the DNA bases, allowing them to "read" the DNA sequence. Most of these base-interactions are made in the major groove, where the bases are most accessible.[84]



The restriction enzyme EcoRV (green) in a complex with its substrate DNA[85]

DNA-modifying enzymes

Nucleases and ligases

Nucleases are enzymes that cut DNA strands by catalyzing the hydrolysis of the phosphodiester bonds. Nucleases that hydrolyse nucleotides from the ends of DNA strands are called exonucleases, while endonucleases cut within strands. The most frequently used nucleases in molecular biology are the restriction endonucleases, which cut DNA at specific sequences. For instance, the EcoRV enzyme shown to the left recognizes the 6-base sequence 5′-GAT|ATC-3′ and makes a cut at the vertical line. In nature, these enzymes protect bacteria against phage infection by digesting the phage DNA when it enters the bacterial cell, acting as part of the restriction modification system.[86] In technology, these sequence-specific nucleases are used in molecular cloning and DNA fingerprinting.

Enzymes called DNA ligases can rejoin cut or broken DNA strands.[87] Ligases are particularly important in lagging strand DNA replication, as they join together the short segments of DNA produced at the replication fork into a complete copy of the DNA template. They are also used in DNA repair and genetic recombination.[87]

Topoisomerases and helicases

Topoisomerases are enzymes with both nuclease and ligase activity. These proteins change the amount of supercoiling in DNA. Some of these enzyme work by cutting the DNA helix and allowing one section to rotate, thereby reducing its level of supercoiling; the enzyme then seals the DNA break.[25] Other types of these enzymes are capable of cutting one DNA helix and then passing a second strand of DNA through this break, before rejoining the helix.[88] Topoisomerases are required for many processes involving DNA, such as DNA replication and transcription.[26]

Helicases are proteins that are a type of molecular motor. They use the chemical energy in nucleoside triphosphates, predominantly ATP, to break hydrogen bonds between bases and unwind the DNA double helix into single strands.[89] These enzymes are essential for most processes where enzymes need to access the DNA bases.

Polymerases

Polymerases are enzymes that synthesize polynucleotide chains from nucleoside triphosphates. The sequence of their products are copies of existing polynucleotide chains - which are called *templates*. These enzymes function by adding nucleotides onto the 3′ hydroxyl group of the previous nucleotide in a DNA strand. Consequently, all polymerases work in a 5′ to 3′ direction.[90] In the active site of these enzymes, the incoming nucleoside triphosphate base-pairs to the template: this allows polymerases to accurately synthesize the complementary strand of their template. Polymerases are classified according to the type of template that they use.

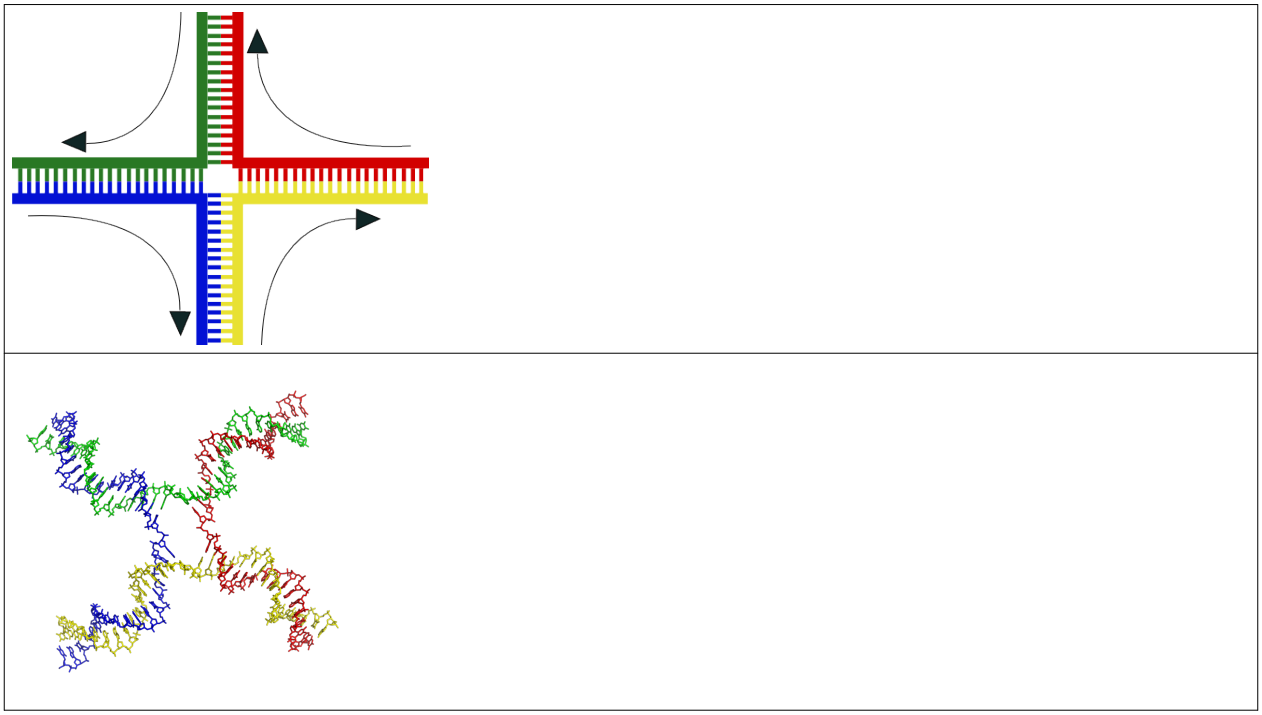
In DNA replication, a DNA-dependent DNA polymerase makes a copy of a DNA sequence. Accuracy is vital in this process, so many of these polymerases have a proofreading activity. Here, the polymerase recognizes the occasional mistakes in the synthesis reaction by the lack of base pairing between the mismatched nucleotides. If a mismatch is detected, a 3′ to 5′ exonuclease activity is activated and the incorrect base removed.[91] In most organisms DNA polymerases function in a large complex called the replisome that contains multiple accessory subunits, such as the DNA clamp or helicases.[92]

RNA-dependent DNA polymerases are a specialized class of polymerases that copy the sequence of an RNA strand into DNA. They include reverse transcriptase, which is a viral enzyme involved in the infection of cells by retroviruses, and telomerase, which is required for the replication of telomeres.[40] [93] Telomerase is an unusual polymerase because it contains its own RNA template as part of its structure.[41]

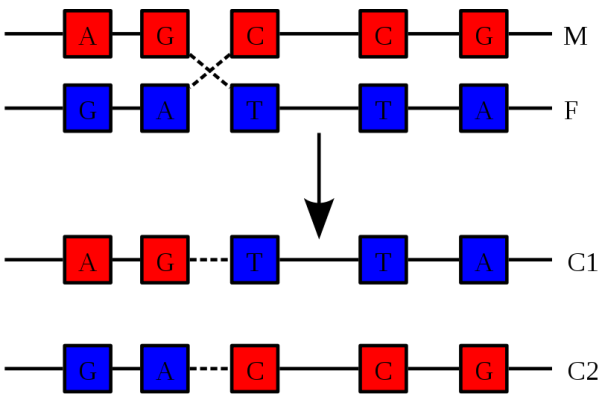
Transcription is carried out by a DNA-dependent RNA polymerase that copies the sequence of a DNA strand into RNA. To begin transcribing a gene, the RNA polymerase binds to a sequence of DNA called a promoter and separates the DNA strands. It then copies the gene sequence into a messenger RNA transcript until it reaches a region of DNA called the terminator, where it halts and detaches from the DNA. As with human DNA-dependent DNA polymerases, RNA polymerase II, the enzyme that transcribes most of the genes in the human genome, operates as part of a large protein complex with multiple regulatory and

accessory subunits.[94]

Genetic recombination



Structure of the Holliday junction intermediate in genetic recombination. The four separate DNA strands are coloured red, blue, green and yellow.[95]



Recombination involves the breakage and rejoining of two chromosomes (M and F) to produce two re-arranged chromosomes (C1 and C2).

A DNA helix usually does not interact with other segments of DNA, and in human cells the different chromosomes even occupy separate areas in the nucleus called "chromosome territories".[96] This physical separation of different chromosomes is important for the ability of DNA to function as a stable repository for information, as one of the few times chromosomes interact is during chromosomal crossover when they recombine. Chromosomal crossover is when two DNA helices break, swap a section and then rejoin.

Recombination allows chromosomes to exchange genetic information and produces new combinations of genes, which increases the efficiency of natural selection and can be important in the rapid evolution of new proteins.[97] Genetic recombination can also be involved in DNA repair, particularly in the cell's response to double-strand breaks.[98]

The most common form of chromosomal crossover is homologous recombination, where the two chromosomes involved share very similar sequences. Non-homologous recombination can be damaging to cells, as it can produce chromosomal translocations and genetic abnormalities. The recombination reaction is catalyzed by enzymes known as *recombinases*, such as RAD51.[99] The first step in recombination is a double-stranded break either caused

by an endonuclease or damage to the DNA.[100] A series of steps catalyzed in part by the recombinase then leads to joining of the two helices by at least one Holliday junction, in which a segment of a single strand in each helix is annealed to the complementary strand in the other helix. The Holliday junction is a tetrahedral junction structure that can be moved along the pair of chromosomes, swapping one strand for another. The recombination reaction is then halted by cleavage of the junction and re-ligation of the released DNA.[101]

Evolution

DNA contains the genetic information that allows all modern living things to function, grow and reproduce. However, it is unclear how long in the 4-billion-year history of life DNA has performed this function, as it has been proposed that the earliest forms of life may have used RNA as their genetic material.[90] [102] RNA may have acted as the central part of early cell metabolism as it can both transmit genetic information and carry out catalysis as part of ribozymes.[103] This ancient RNA world where nucleic acid would have been used for both catalysis and genetics may have influenced the evolution of the current genetic code based on four nucleotide bases. This would occur since the number of unique bases in such an organism is a trade-off between a small number of bases increasing replication accuracy and a large number of bases increasing the catalytic efficiency of ribozymes.[104]

Unfortunately, there is no direct evidence of ancient genetic systems, as recovery of DNA from most fossils is impossible. This is because DNA will survive in the environment for less than one million years and slowly degrades into short fragments in solution.[105] Claims for older DNA have been made, most notably a report of the isolation of a viable bacterium from a salt crystal 250-million years old,[106] but these claims are controversial.[107] [108]

Uses in technology

Genetic engineering

Methods have been developed to purify DNA from organisms, such as phenol-chloroform extraction and manipulate it in the laboratory, such as restriction digests and the polymerase chain reaction. Modern biology and biochemistry make intensive use of these techniques in recombinant DNA technology. Recombinant DNA is a man-made DNA sequence that has been assembled from other DNA sequences. They can be transformed into organisms in the form of plasmids or in the appropriate format, by using a viral vector.[109] The genetically modified organisms produced can be used to produce products such as recombinant proteins, used in medical research,[110] or be grown in agriculture.[111] [112]

Forensics

Forensic scientists can use DNA in blood, semen, skin, saliva or hair found at a crime scene to identify a matching DNA of an individual, such as a perpetrator. This process is called genetic fingerprinting, or more accurately, DNA profiling. In DNA profiling, the lengths of variable sections of repetitive DNA, such as short tandem repeats and minisatellites, are compared between people. This method is usually an extremely reliable technique for identifying a matching DNA.[113] However, identification can be complicated if the scene is contaminated with DNA from several people.[114] DNA profiling was developed in 1984 by British geneticist Sir Alec Jeffreys,[115] and first used in forensic science to convict Colin

Pitchfork in the 1988 Enderby murders case.[116]

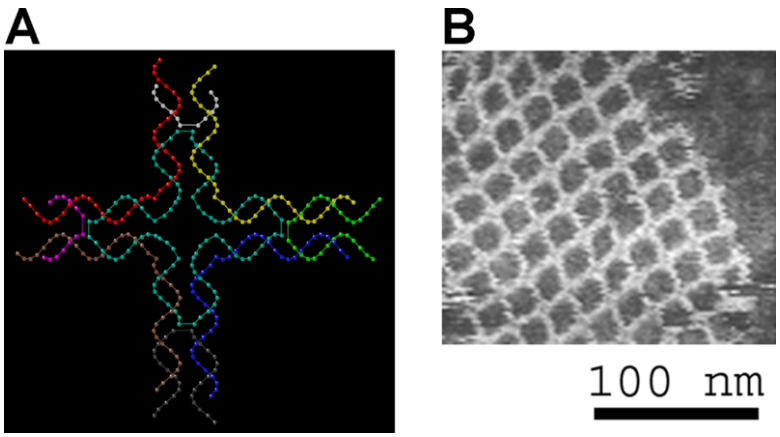
People convicted of certain types of crimes may be required to provide a sample of DNA for a database. This has helped investigators solve old cases where only a DNA sample was obtained from the scene. DNA profiling can also be used to identify victims of mass casualty incidents.[117] On the other hand, many convicted people have been released from prison on the basis of DNA techniques, which were not available when a crime had originally been committed.

Bioinformatics

Bioinformatics involves the manipulation, searching, and data mining of DNA sequence data. The development of techniques to store and search DNA sequences have led to widely applied advances in computer science, especially string searching algorithms, machine learning and database theory.[118] String searching or matching algorithms, which find an occurrence of a sequence of letters inside a larger sequence of letters, were developed to search for specific sequences of nucleotides.[119] In other applications such as text editors, even simple algorithms for this problem usually suffice, but DNA sequences cause these algorithms to exhibit near-worst-case behaviour due to their small number of distinct characters. The related problem of sequence alignment aims to identify homologous sequences and locate the specific mutations that make them distinct. These techniques, especially multiple sequence alignment, are used in studying phylogenetic relationships and protein function.[120] Data sets representing entire genomes' worth of DNA sequences, such as those produced by the Human Genome Project, are difficult to use without annotations, which label the locations of genes and regulatory elements on each chromosome. Regions of DNA sequence that have the characteristic patterns associated with protein- or RNA-coding genes can be identified by gene finding algorithms, which allow researchers to predict the presence of particular gene products in an organism even before they have been isolated experimentally.[121]

DNA nanotechnology

DNA nanotechnology uses the unique molecular recognition properties of DNA and other nucleic acids to create self-assembling branched DNA complexes with useful properties.[123] DNA is thus used as a structural material rather than as a carrier of biological information. This has led to the creation of two-dimensional periodic lattices (both tile-based as well as using the "DNA origami" method) as well as



The DNA structure at left (schematic shown) will self-assemble into the structure visualized by atomic force microscopy at right. DNA nanotechnology is the field which seeks to design nanoscale structures using the molecular recognition properties of DNA molecules. Image from Strong, 2004.[122]

three-dimensional structures in the shapes of polyhedra.[124] Nanomechanical devices and algorithmic self-assembly have also been demonstrated,[125] and these DNA structures have been used to template the arrangement of other molecules such as gold nanoparticles and streptavidin proteins.[126]

History and anthropology

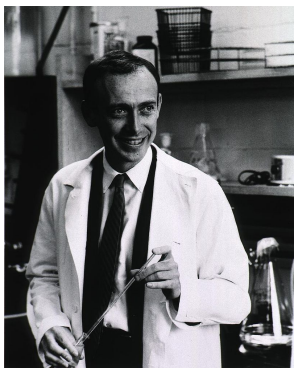
Because DNA collects mutations over time, which are then inherited, it contains historical information and by comparing DNA sequences, geneticists can infer the evolutionary history of organisms, their phylogeny.[127] This field of phylogenetics is a powerful tool in evolutionary biology. If DNA sequences within a species are compared, population geneticists can learn the history of particular populations. This can be used in studies ranging from ecological genetics to anthropology; for example, DNA evidence is being used to try to identify the Ten Lost Tribes of Israel.[128] [129]

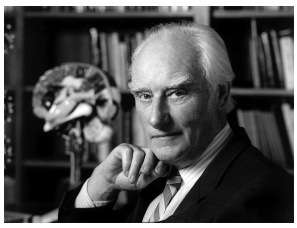
DNA has also been used to look at modern family relationships, such as establishing family relationships between the descendants of Sally Hemings and Thomas Jefferson. This usage is closely related to the use of DNA in criminal investigations detailed above. Indeed, some criminal investigations have been solved when DNA from crime scenes has matched relatives of the guilty individual.[130]

History of DNA research

DNA was first isolated by the Swiss physician Friedrich Miescher who, in 1869, discovered a microscopic substance in the pus of discarded surgical bandages. As it resided in the nuclei of cells, he called it "nuclein".[131] In 1919, Phoebus Levene identified the base, sugar and phosphate nucleotide unit.[132] Levene suggested that DNA consisted of a string of nucleotide units linked together through the phosphate groups. However, Levene thought the chain was short and the bases repeated in a fixed order. In 1937 William Astbury produced the first X-ray diffraction patterns that showed that DNA had a regular structure.[133]

In 1928, Frederick Griffith discovered that traits of the "smooth" form of the *Pneumococcus* could be transferred to the "rough" form of the same bacteria by mixing killed "smooth" bacteria with the live "rough" form.[134] This system provided the first clear suggestion that DNA carried genetic information—the Avery-MacLeod-McCarty experiment—when Oswald Avery, along with coworkers Colin MacLeod and Maclyn McCarty, identified DNA as the transforming principle in 1943.[135] DNA's role in heredity was confirmed in 1952, when Alfred Hershey and Martha Chase in the Hershey-Chase experiment showed that DNA is the genetic material of the T2 phage.[136]


James D. Watson

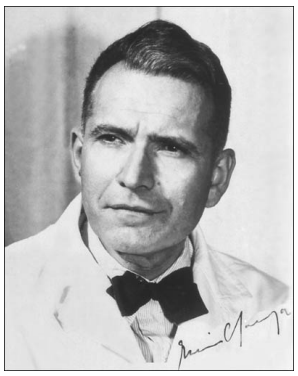

Francis Crick

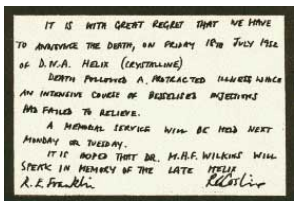

Francis Crick


Rosalind Franklin


Raymond Gosling


Maurice F.Wilkins


Erwin Chargaff


IT IS WITH GREAT REGRET THAT WE HAVE TO ANNOUNCE THE DEATH, ON FRIDAY 16TH JULY 1958 OF D.N.A. HELIX (CRYSTALLINE)
DEATH FOLLOWED A PROTRACTED ILLNESS WHICH AN INTENSIVE COURSE OF BIOLOGICAL PHYSICISTS HAS FAILED TO RELIEVE.
A MEMORIAL SERVICE WILL BE HELD NEXT MONDAY OR TUESDAY.
IT IS HOPED THAT DR. M.H.F. WILKINS WILL SPEAK IN MEMORY OF THE LATE HELIX
R.E. Franklin
DNA Helix controversy

In 1953 James D. Watson and Francis Crick suggested what is now accepted as the first correct double-helix model of DNA structure in the journal *Nature*.[6] Their double-helix, molecular model of DNA was then based on a single X-ray diffraction image (labeled as "Photo 51")[137] taken by Rosalind Franklin and Raymond Gosling in May 1952, as well as the information that the DNA bases were paired—also obtained through private communications from Erwin Chargaff in the previous years. Chargaff's rules played a very important role in establishing double-helix configurations for B-DNA as well as A-DNA.

Experimental evidence supporting the Watson and Crick model were published in a series of five articles in the same issue of *Nature*.[138] Of these, Franklin and Gosling's paper was the first publication of their own X-ray diffraction data and original analysis method that partially supported the Watson and Crick model[29] [139] ; this issue also contained an article on DNA structure by Maurice Wilkins and two of his colleagues, whose analysis and **in vivo** B-DNA X-ray patterns also supported the presence *in vivo* of the double-helical DNA configurations as proposed by Crick and Watson for their double-helix molecular model of DNA in the previous two pages of *Nature*.[30] In 1962, after Franklin's death, Watson, Crick, and Wilkins jointly received the Nobel Prize in Physiology or Medicine.[140] Unfortunately, Nobel rules of the time allowed only living recipients, but a vigorous debate continues on who should receive credit for the discovery.[141]

In an influential presentation in 1957, Crick laid out the "Central Dogma" of molecular biology, which foretold the relationship between DNA, RNA, and proteins, and articulated

the "adaptor hypothesis".[142] Final confirmation of the replication mechanism that was implied by the double-helical structure followed in 1958 through the Meselson-Stahl experiment.[143] Further work by Crick and coworkers showed that the genetic code was based on non-overlapping triplets of bases, called codons, allowing Har Gobind Khorana, Robert W. Holley and Marshall Warren Nirenberg to decipher the genetic code.[144] These findings represent the birth of molecular biology.

See also

- Molecular Structure of Nucleic Acids: A Structure for Deoxyribose Nucleic Acid
- → Molecular models of DNA
- DNA microarray
- DNA sequencing
- → Paracrystal model and theory
- X-ray scattering
- Crystallography
- X-ray crystallography
- Genetic disorder
- Junk DNA
- Nucleic acid analogues
- Nucleic acid methods
- Nucleic acid modeling
- Nucleic Acid Notations
- Phosphoramidite
- Plasmid
- Polymerase chain reaction
- *Proteopedia DNA* [145]
- Southern blot
- Triple-stranded DNA

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Further reading

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External links

- DNA (http://www.dmoz.org/Science/Biology/Biochemistry_and_Molecular_Biology/Biomolecules/Nucleic_Acids/DNA//) at the Open Directory Project
- DNA binding site prediction on protein (http://pipe.scs.fsu.edu/displar.html)
- DNA coiling to form chromosomes (http://biostudio.com/c_ education mac.htm)
- DNA from the Beginning (http://www.dnaftb.org/dnaftb/) Another DNA Learning Center site on DNA, genes, and heredity from Mendel to the human genome project.
- DNA Lab, demonstrates how to extract DNA from wheat using readily available equipment and supplies. (http://ca.youtube.com/watch?v=iyb7fwduuGM)
- DNA the Double Helix Game (http://nobelprize.org/educational_games/medicine/dna_double_helix/) From the official Nobel Prize web site

- DNA under electron microscope (http://www.fidelitysystems.com/Unlinked_DNA.html)
- Dolan DNA Learning Center (http://www.dnalc.org/)
- Double Jelix: 50 years of DNA (http://www.nature.com/nature/dna50/archive.html), *Nature*
- Double Helix 1953–2003 (http://www.ncbe.reading.ac.uk/DNA50/) National Centre for Biotechnology Education
- Francis Crick and James Watson talking on the BBC in 1962, 1972, and 1974 (http://www.bbc.co.uk/bbcfour/audiointerviews/profilepages/crickwatson1.shtml)
- Genetic Education Modules for Teachers (http://www.genome.gov/10506718) — *DNA from the Beginning* Study Guide
- Guide to DNA cloning (http://www.blackwellpublishing.com/trun/artwork/Animations/cloningexp/cloningexp.html)
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- PDB Molecule of the Month *pdb23_1 (http://www.rcsb.org/pdb/static.do?p=education_discussion/molecule_of_the_month/pdb23_1.html)*
- Rosalind Franklin's contributions to the study of DNA (http://mason.gmu.edu/~emoody/rfranklin.html)
- The Register of Francis Crick Personal Papers 1938 - 2007 (http://orpheus.ucsd.edu/speccoll/testing/html/mss0660a.html#abstract) at Mandeville Special Collections Library, Geisel Library, University of California, San Diego
- The Secret Life of DNA - DNA Music compositions (http://www.tjmitchell.com/stuart/dna.html)
- U.S. National DNA Day (http://www.genome.gov/10506367) — watch videos and participate in real-time chat with top scientists
- " Clue to chemistry of heredity found (http://www.nytimes.com/packages/pdf/science/dna-article.pdf)". *The New York Times*. Saturday, June 13, 1953. http://www.nytimes.com/packages/pdf/science/dna-article.pdf. The first American newspaper coverage of the discovery of the DNA structure.

Paracrystalline

Paracrystalline materials are defined as having short and medium range ordering in their lattice (similar to the liquid crystal phases) but lacking long-range ordering at least in one direction.[1]

Ordering is the regularity in which atoms appear in a predictable lattice, as measured from one point. In a highly ordered, perfectly crystalline material, or single crystal, the location of every atom in the structure can be described exactly measuring out from a single origin. Conversely, in a disordered structure such as a liquid or amorphous solid, the location of the first and perhaps second nearest neighbors can be described from an origin (with some degree of uncertainty) and the ability to predict locations decreases rapidly from there out. The distance at which atom locations can be predicted is referred to as the correlation length ξ. A paracrystalline material exhibits correlation somewhere between the fully amorphous and fully crystalline.

The primary, most accessible source of crystallinity information is X-ray diffraction, although other techniques may be needed to observe the complex structure of paracrystalline materials, such as fluctuation electron microscopy [2] in combination with Density of states modeling[3] of electronic and vibrational states.

Paracrystalline Model

The paracrystalline model is a revision of the Continuous Random Network model first proposed by W. H. Zachariasen in 1932 [4] . The paracrystal model is defined as highly strained, microcrystalline grains surrounded by fully amorphous material [5] . This is a higher energy state then the continuous random network model. The important distinction between this model and the microcrystalline phases is the lack of defined grain boundaries and highly strained lattice parameters, which makes calculations of molecular and lattice dynamics difficult. A general theory of paracrystals has been formulated in a basic textbook[6] , and then further developed/refined by various authors.

Applications

The paracrystal model has been useful, for example, in describing the state of partially amorphous semiconductor materials after deposition. It has also been successfully applied to: synthetic polymers, liquid crystals, biopoloymers [7] ,[8] and biomembranes[9] .

See also

- X-ray scattering
- Amorphous solid
- Single Crystal
- Polycrystalline
- Crystallography
- → DNA
- X-ray pattern of a B-DNA Paracrystal [10]

Notes

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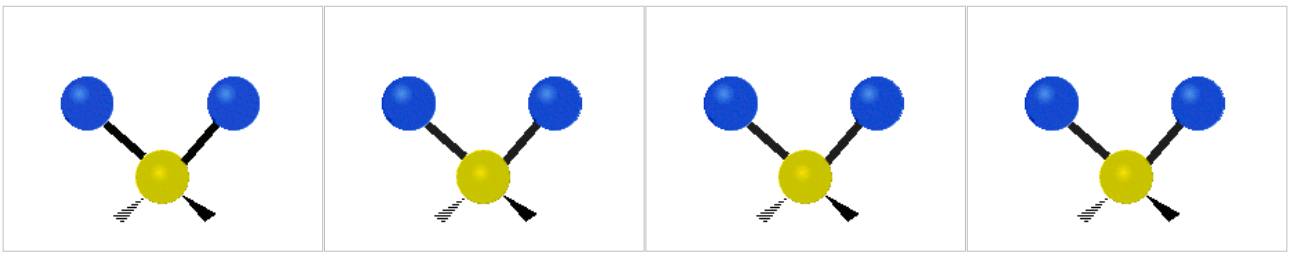
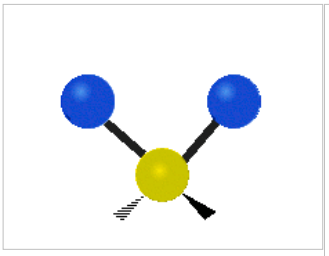
[10] http://commons.wikimedia.org/wiki/File:ABDNAxrgpj.jpg

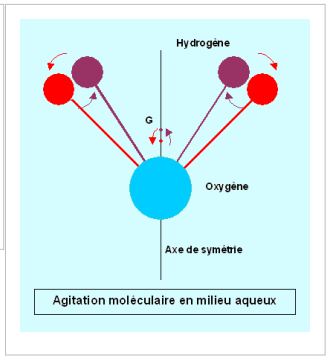
Vibrational circular dichroism

Vibrational circular dichroism (VCD) spectroscopy is basically circular dichroism spectroscopy in the infrared and near infrared ranges[1] . Because VCD is sensitive to the mutual orientation of distinct groups in a molecule, it provides three-dimensional structural information. Thus, it is a powerful technique as VCD spectra of enantiomers can be simulated using *ab initio* calculations, thereby allowing the identification of absolute configurations of small molecules in solution from VCD spectra. Among such quantum computations of VCD spectra resulting from the chiral properties of small organic molecules are those based on density functional theory (DFT) and gauge-invariant atomic orbitals (GIAO). As a simple example of the experimental results that were obtained by VCD are the spectral data obtained within the carbon-hydrogen (C-H) stretching region of 21 amino acids in heavy water solutions. Measurements of vibrational optical activity (VOA) have thus numerous applications, not only for small molecules, but also for large and complex biopolymers such as muscle proteins (myosin, for example) and → DNA.

Vibrational modes



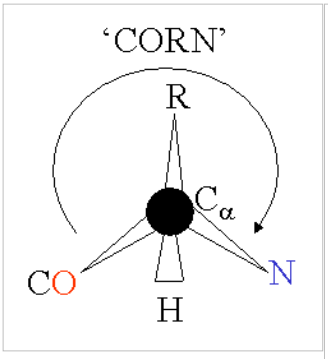


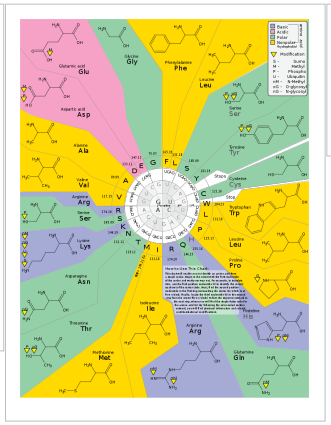


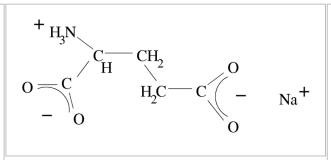
VCD of peptides and proteins

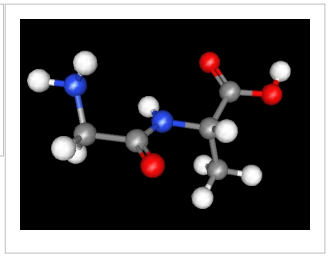
Extensive VCD studies have been reported for both polypeptides and several proteins in solution[2] [3] [4] ; several recent reviews were also compiled[5] [6] [7] [8] . An extensive but not comprehensive VCD publications list is also provided in the "References" section. The published reports over the last 22 years have established VCD as a powerful technique with improved results over those previously obtained by visible/UV circular dichroism (CD) or optical rotatory dispersion (ORD) for proteins and nucleic acids.

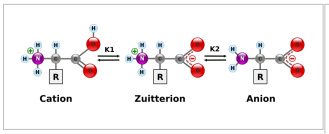
Amino acid and polypeptide structures

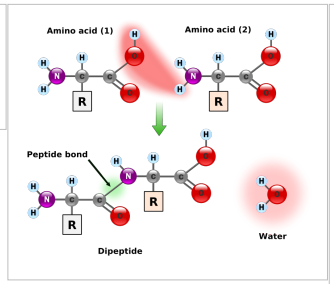


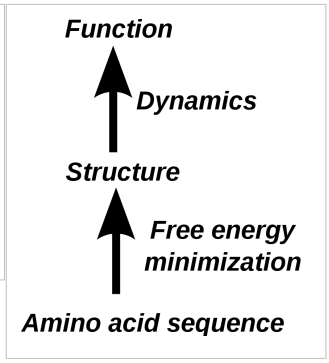


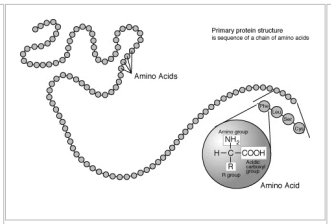


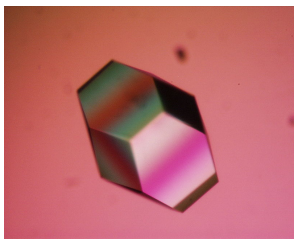


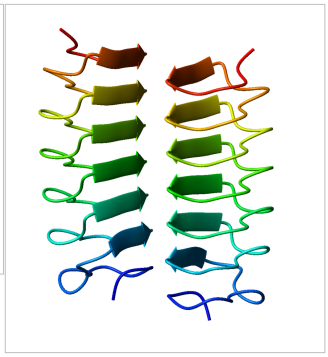


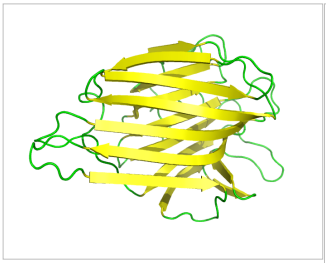


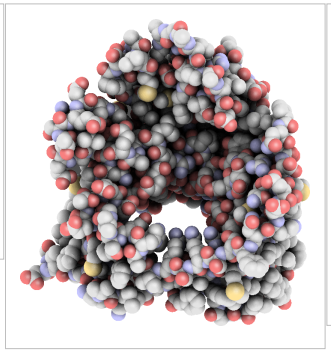


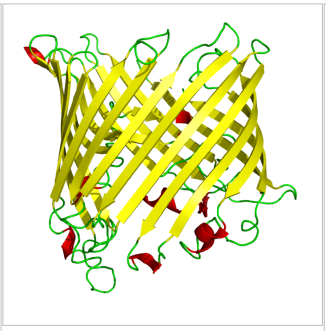

Primary protein structure
is sequence of a chain of amino acids
Amino Acids
Amino Acid

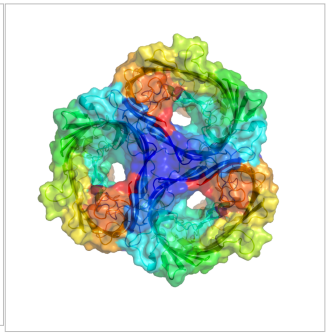


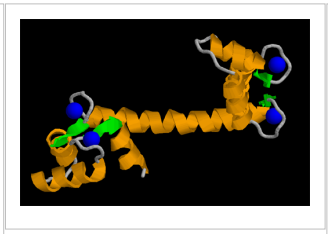


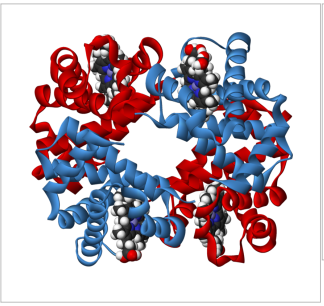


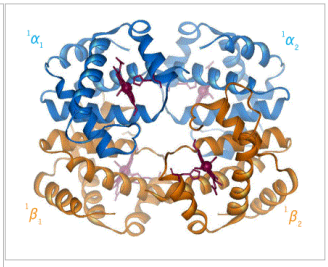








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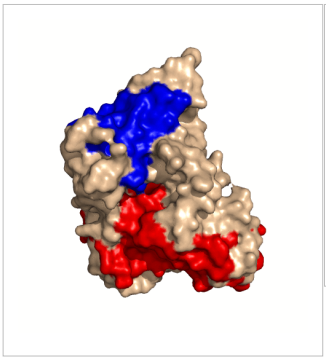
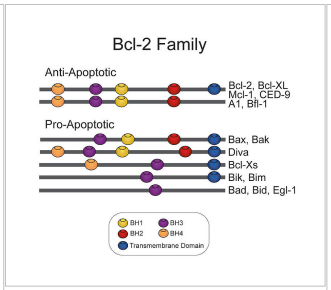
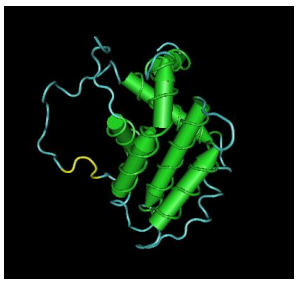
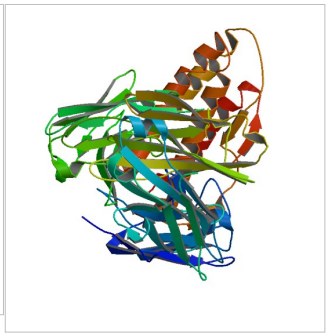
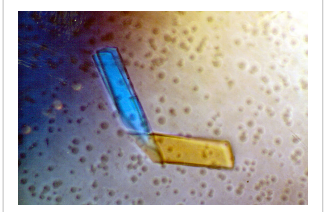
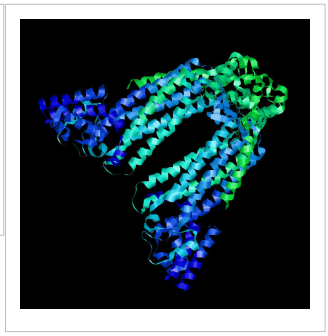



Bcl-2 Family
Anti-Apoptotic
Bcl-2, Bcl-XL
Mcl-1, CED-9
A1, Bfl-1
Pro-Apoptotic
Bax, Bak
Diva
Bcl-Xs
Bik, Bim
Bad, Bid, Egl-1
BH1
BH3
BH2
BH4
Transmembrane Domain







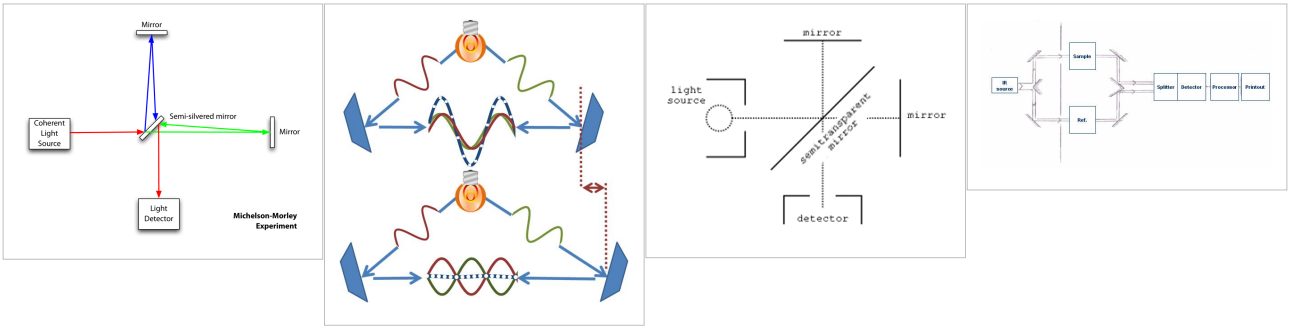


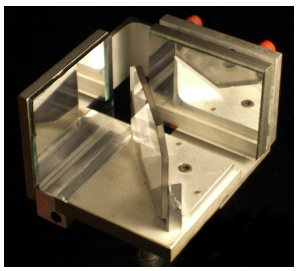
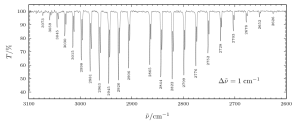
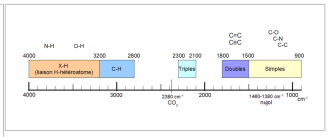
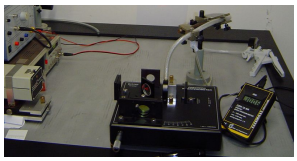
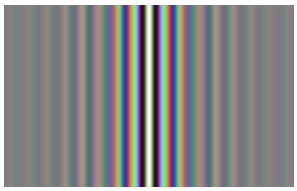
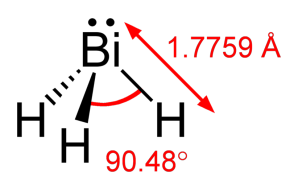
VCD of nucleic acids

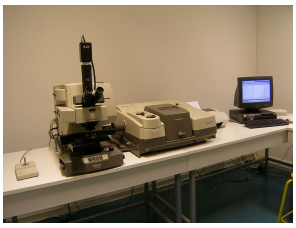
VCD spectra of nucleotides, synthetic polynucleotides and several nucleic acids, including DNA, have been reported and assigned in terms of the type and number of helices present in A- , B-, and Z- DNA.

VCD Instrumentation

For biopolymers such as proteins and nucleic acids, the difference in absorbance between the levo- and dextro- configurations is five orders of magnitude smaller than the corresonding (unpolarized) absorbance. Therefore, VCD of biopolymers requires the use of very sensitive, specially built instrumentation as well as time-averaging over relatively long intervals of time even with such sensitive VCD spectrometers. Most CD instruments produce left- and right- circularly polarized light which is then either sine-wave or square-wave modulated, with subsequent phase-sensitive detection and lock-in amplification of the detected signal. In the case of FT-VCD, a photo-elastic modulator (PEM) is employed in conjunction with an FT-IR interferometer set-up. An example is that of a Bomem model MB-100 FT-IR interferometer equipped with additional polarizing optics/ accessories needed for recording VCD spectra. A parallel beam emerges through a side port of the interferometer which passes first through a wire grid linear polarizer and then through an octagonal-shaped ZnSe crystal PEM which modulates the polarized beam at a fixed, lower frequency such as 37.5 kHz. A mechanically stressed crystal such as ZnSe exhibits birefringence when stressed by an adjacent piezoelectric transducer. The linear polarizer is positioned close to, and at 45 degrees, with respect to the ZnSe crystal axis. The polarized radiation focused onto the detector is doubly modulated, both by the PEM and by the interferometer setup. A very low noise detector, such as MCT (HgCdTe), is also selected for the VCD signal phase-sensitive detection. Quasi-complete commercial FT-VCD instruments are also available from a few manufacturers but these are quite expensive and also have to be still considered as being at the prototype stage. To prevent detector saturation an appropriate, long wave pass filter is placed before the very low noise MCT detector, which allows only radiation below 1750 cm^{-1} to reach the MCT detector; the latter however measures radiation only down to 750 cm^{-1}. FT-VCD spectra accumulation of the selected sample solution is then carried out, digitized and stored by an in-line computer. Published reviews that compare various VCD methods are also available.[9] [10]





Magnetic VCD

VCD spectra have also been reported in the presence of an applied external magnetic field[11] . This method can enhance the VCD spectral resolution for small molecules[12] [13] [14] [15] [16] .

Raman optical activity (ROA)

ROA is a technique complementary to VCD especially useful in the 50--1600 cm^{-1} spectral region; it is considered as the technique of choice for determining optical activity for photon energies less then 600 cm^{-1}.

Notes

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See also

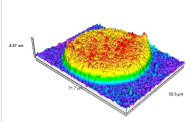
- Circular dichroism
- Birefringence
- Optical rotatory dispersion
- IR spectroscopy
- Polarization
- Proteins
- Nucleic Acids
- → DNA
- → Molecular models of DNA
- DNA structure
- Protein structure
- Amino acids
- Density functional theory
- Quantum chemistry
- Raman optical activity (ROA)

DNA Molecular Dynamics

Molecular models of DNA

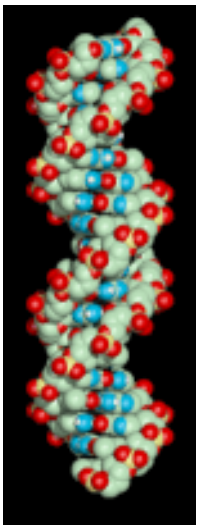
Molecular models of DNA structures are representations of the molecular geometry and topology of Deoxyribonucleic acid (→ DNA) molecules using one of several means, such as: closely packed spheres (CPK models) made of plastic, metal wires for 'skeletal models', graphic computations and animations by computers, artistic rendering, and so on, with the aim of simplifying and presenting the essential, physical and chemical, properties of DNA molecular structures either *in vivo* or *in vitro*. Computer molecular models also allow animations and molecular dynamics simulations that are very important for understanding how DNA functions *in vivo*. Thus, an old standing dynamic problem is how DNA "self-replication" takes place in living cells that should involve transient uncoiling of supercoiled DNA fibers. Although DNA consists of relatively rigid, very large elongated biopolymer molecules called "fibers" or chains (that are made of repeating nucleotide units of four basic types, attached to deoxyribose and phosphate groups), its molecular structure *in vivo* undergoes dynamic configuration changes that involve dynamically attached water molecules and ions. Supercoiling, packing with histones in chromosome structures, and other such supramolecular aspects also involve *in vivo* DNA topology which is even more complex than DNA molecular geometry, thus turning molecular modeling of DNA into an especially challenging problem for both molecular biologists and biotechnologists. Like other large molecules and biopolymers, DNA often exists in multiple stable geometries (that is, it exhibits conformational isomerism) and configurational, quantum states which are close to each other in energy on the potential energy surface of the DNA molecule. Such geometries can also be computed, at least in principle, by employing *ab initio* quantum chemistry methods that have high accuracy for small molecules. Such quantum geometries define an important class of *ab initio* molecular models of DNA whose exploration has barely started.

In an interesting twist of roles, the DNA molecule itself was proposed to be utilized for quantum computing. Both DNA nanostructures as well as DNA 'computing' biochips have been built (see biochip image at right).



DNA computing biochip:3D

The more advanced, computer-based molecular models of DNA involve → molecular dynamics simulations as well as quantum mechanical computations of vibro-rotations, delocalized molecular orbitals (MOs), electric dipole moments, hydrogen-bonding, and so on.



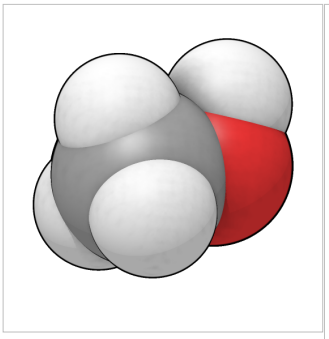
Spinning DNA generic model.

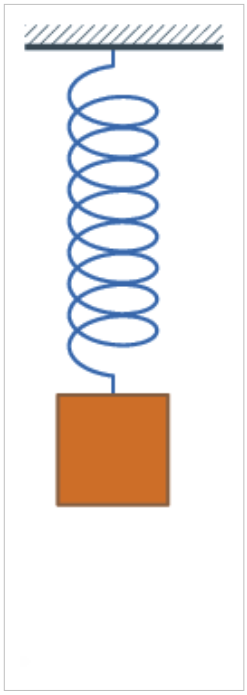
Importance

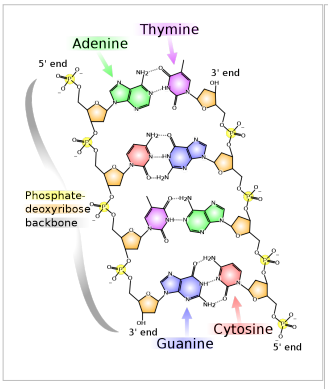
From the very early stages of structural studies of DNA by X-ray diffraction and biochemical means, molecular models such as the Watson-Crick double-helix model were successfully employed to solve the 'puzzle' of DNA structure, and also find how the latter relates to its key functions in living cells. The first high quality X-ray diffraction patterns of A-DNA were reported by Rosalind Franklin and Raymond Gosling in 1953[1] . The first calculations of the Fourier transform of an atomic helix were reported one year earlier by Cochran, Crick and Vand [2] , and were followed in 1953 by the computation of the Fourier transform of a coiled-coil by Crick[3] . The first reports of a double-helix molecular model of B-DNA structure were made by Watson and Crick in 1953[4] [5] . Last-but-not-least, Maurice F. Wilkins, A. Stokes and H.R. Wilson, reported the first X-ray patterns of *in vivo* B-DNA in partially oriented salmon sperm heads [6] . The development of the first correct double-helix molecular model of DNA by Crick and Watson may not have been possible without the biochemical evidence for the nucleotide base-pairing ([A---T]; [C---G]), or Chargaff's rules[7] [8] [9] [10] [11] [12] .

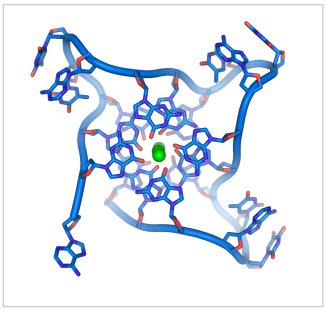
Examples of DNA molecular models

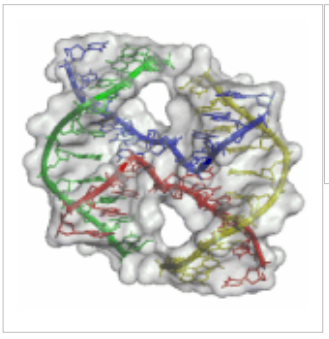
Animated molecular models allow one to visually explore the three-dimensional (3D) structure of DNA. The first DNA model is a space-filling, or CPK, model of the DNA double-helix whereas the third is an animated wire, or skeletal type, molecular model of DNA. The last two DNA molecular models in this series depict quadruplex DNA [13] that may be involved in certain cancers[14] [15] . The last figure on this panel is a molecular model of hydrogen bonds between water molecules in ice that are similar to those found in DNA.

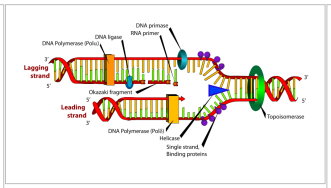


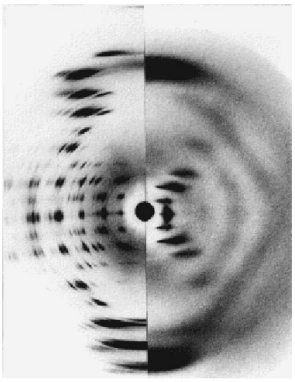



Thymine
Adenine
5' end
3' end
Phosphate-
deoxyribose
backbone
3' end
Guanine
Cytosine
5' end

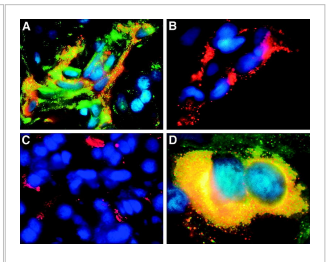


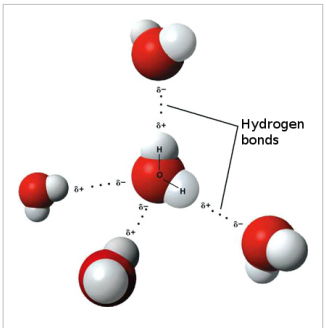



Lagging strand
Leading strand
Okazaki fragment
DNA Polymerase (Pol I)
DNA ligase
DNA primase
RNA primer
DNA Polymerase (Pol III)
Helicase
Single strand. Binding proteins
Topoisomerase

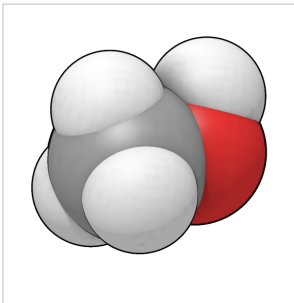


A-DNA B-DNA


A
B
C
D



- Spacefilling model or CPK model - a molecule is represented by overlapping spheres representing the atoms.

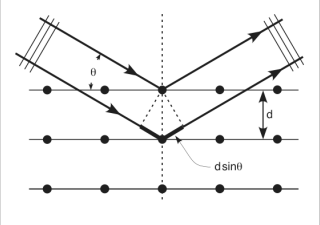


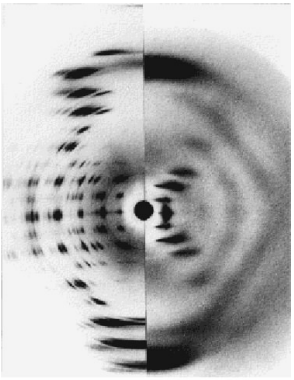
Images for DNA Structure Determination from X-Ray Patterns

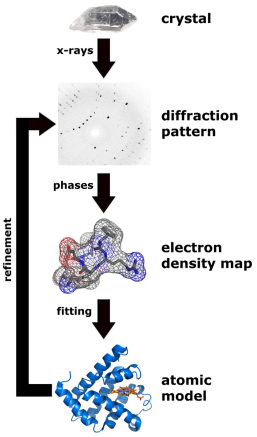
The following images illustrate both the principles and the main steps involved in generating structural information from X-ray diffraction studies of oriented DNA fibers with the help of molecular models of DNA that are combined with crystallographic and mathematical analysis of the X-ray patterns. From left to right the gallery of images shows:

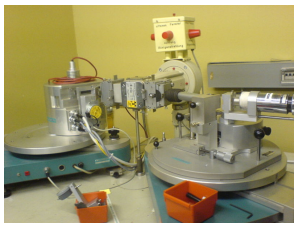
- *First row*:
- 1. Constructive X-ray interference, or diffraction, following Bragg's Law of X-ray "*reflection by the crystal planes*";
- 2. A comparison of A-DNA (crystalline) and highly hydrated B-DNA (paracrystalline) X-ray diffraction, and respectively, X-ray scattering patterns (courtesy of Dr. Herbert R. Wilson, FRS- see refs. list);
- 3. Purified DNA precipitated in a water jug;
- 4. The major steps involved in DNA structure determination by X-ray crystallography showing the important role played by molecular models of DNA structure in this iterative, structure--determination process;
- *Second row*:
- 5. Photo of a modern X-ray diffractometer employed for recording X-ray patterns of DNA with major components: X-ray source, goniometer, sample holder, X-ray detector and/or plate holder;
- 6. Illustrated animation of an X-ray goniometer;
- 7. X-ray detector at the SLAC synchrotron facility;
- 8. Neutron scattering facility at ISIS in UK;
- *Third and fourth rows*: *Molecular models of DNA structure at various scales*; figure #11 is an actual electron micrograph of a DNA fiber bundle, presumably of a single

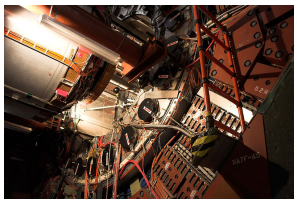
bacterial chromosome loop.

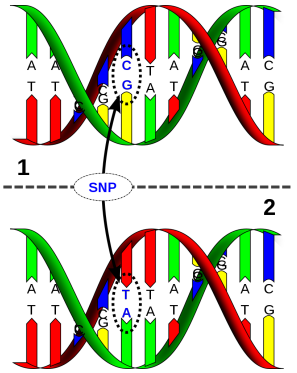


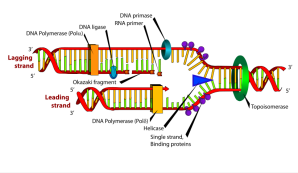


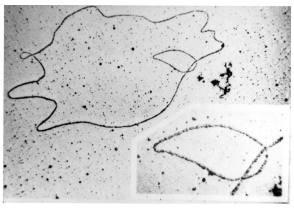


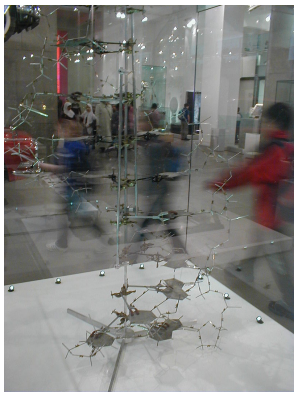


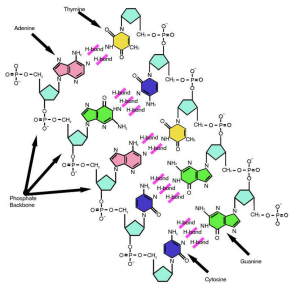


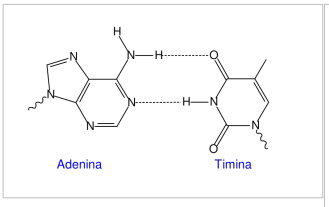


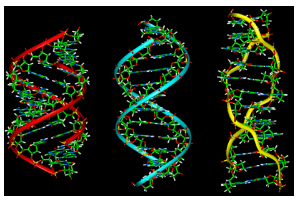


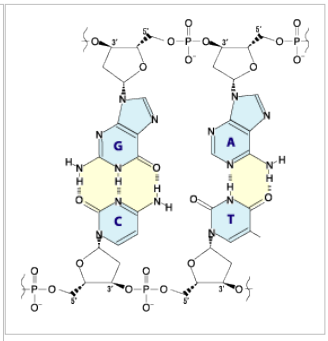


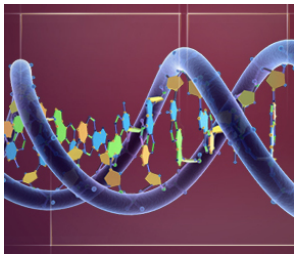


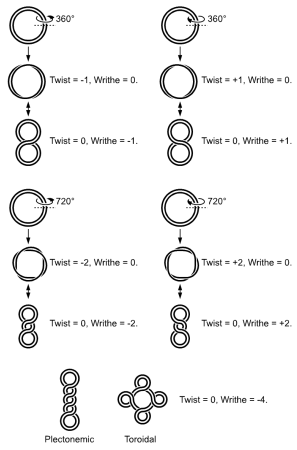


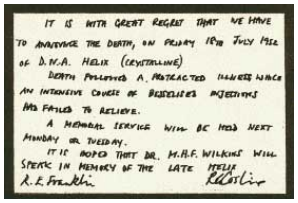






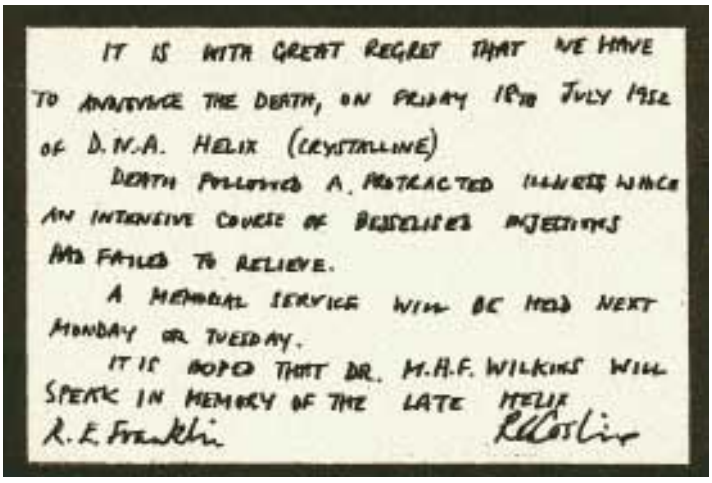






Paracrystalline lattice models of B-DNA structures

A → paracrystalline lattice, or paracrystal, is a molecular or atomic lattice with significant amounts (e.g., larger than a few percent) of partial disordering of molecular arranegements. Limiting cases of the paracrystal model are nanostructures, such as glasses, liquids, etc., that may possess only local ordering and no global order. Liquid crystals also have paracrystalline rather than crystalline structures.



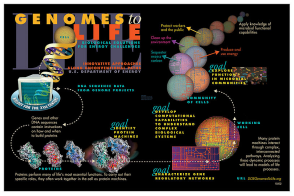
DNA Helix controversy in 1952

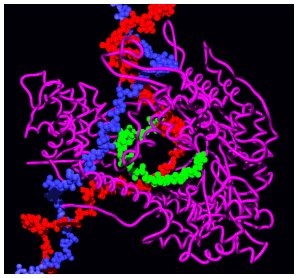
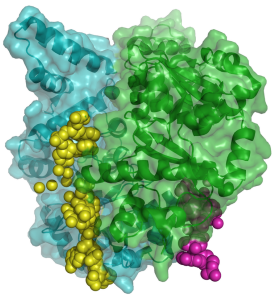
Highly hydrated B-DNA occurs naturally in living cells in such a paracrystalline state, which is a dynamic one in spite of the relatively rigid DNA double-helix stabilized by parallel hydrogen bonds between the nucleotide base-pairs in the two complementary, helical DNA chains (see figures). For simplicity most DNA molecular models ommit both water and ions dynamically bound to B-DNA, and are thus less useful for understanding the dynamic behaviors of B-DNA *in vivo*. The physical and mathematical analysis of X-ray[16] [17] and spectroscopic data for paracrystalline B-DNA is therefore much more complicated than that of crystalline, A-DNA X-ray diffraction patterns. The paracrystal model is also important for DNA technological applications such as DNA nanotechnology. Novel techniques that combine X-ray diffraction of DNA with X-ray microscopy in hydrated living cells are now also being developed (see, for example, "Application of X-ray microscopy in the analysis of living hydrated cells" [18]).

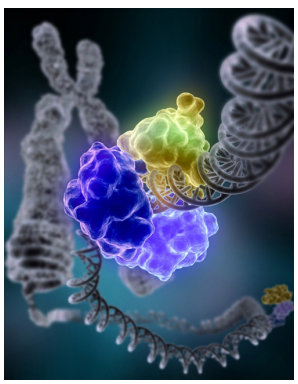
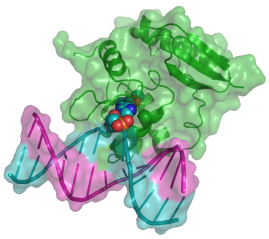
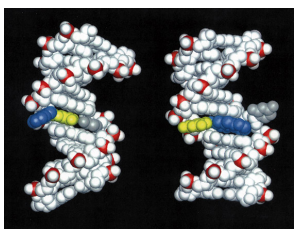
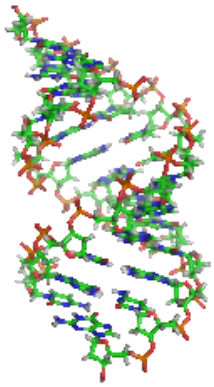
Genomic and Biotechnology Applications of DNA molecular modeling

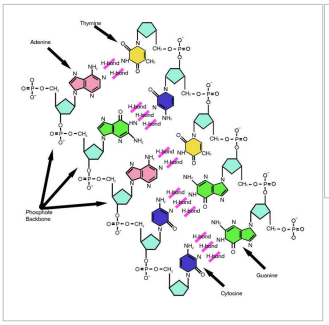
The following gallery of images illustrates various uses of DNA molecular modeling in Genomics and Biotechnology research applications from DNA repair to PCR and DNA nanostructures; each slide contains its own explanation and/or details. The first slide presents an overview of DNA applications, including DNA molecular models, with emphasis on Genomics and Biotechnology.

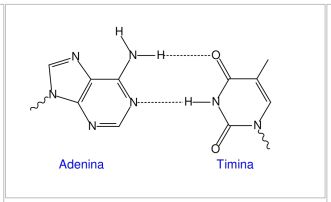
Gallery: DNA Molecular modeling applications

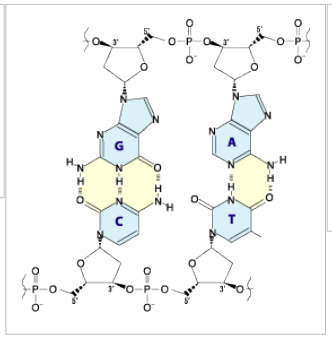


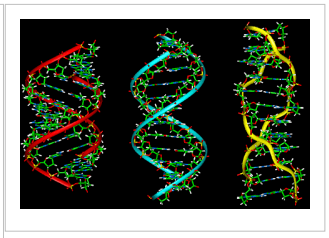



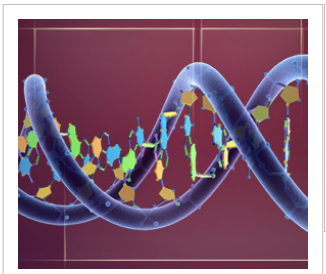





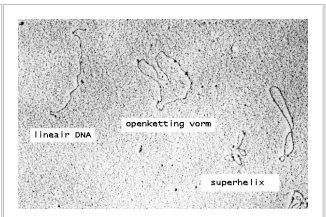

Thymine
Adenine
Phosphate Backbone
Guanine
Cytosine

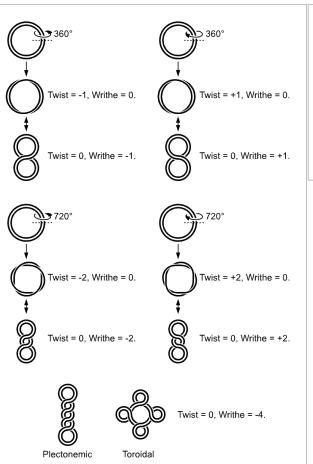

Adenina
Timina

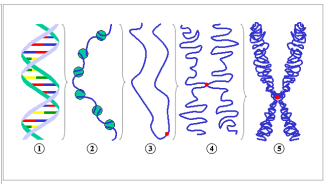

G
C
A
T

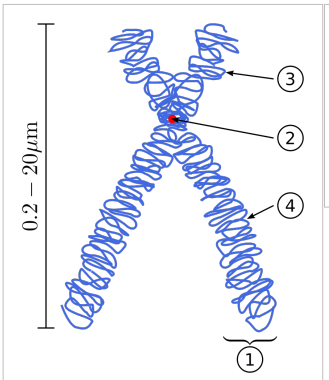


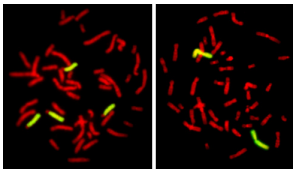


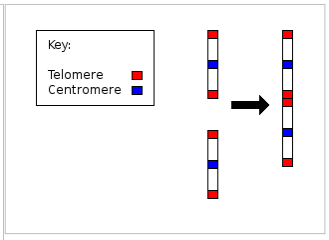

linear DNA
openkettling vorm
superhelix

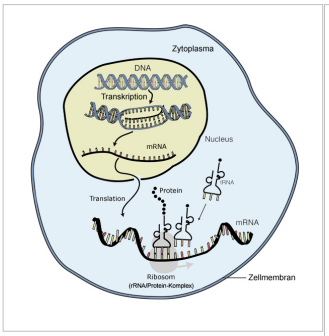

360°
Twist = -1, Writhe = 0.
Twist = 0, Writhe = -1.
360°
Twist = +1, Writhe = 0.
Twist = 0, Writhe = +1.
720°
Twist = -2, Writhe = 0.
Twist = 0, Writhe = -2.
720°
Twist = +2, Writhe = 0.
Twist = 0, Writhe = +2.
Twist = 0, Writhe = -4.
Plectonemic
Toroidal

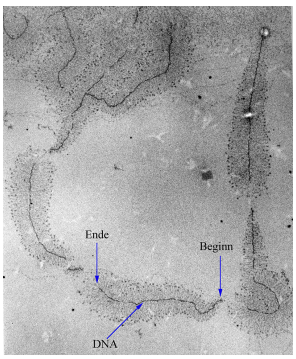

1
2
3
4
5

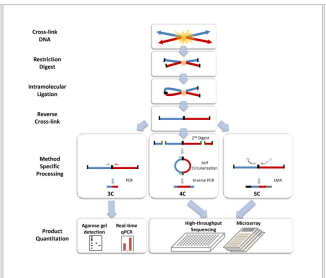

0.2 – 20µm
1
2
3
4

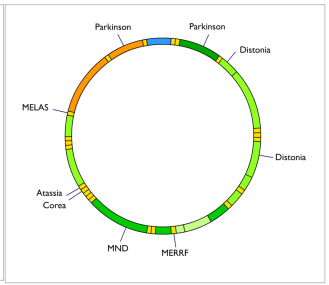


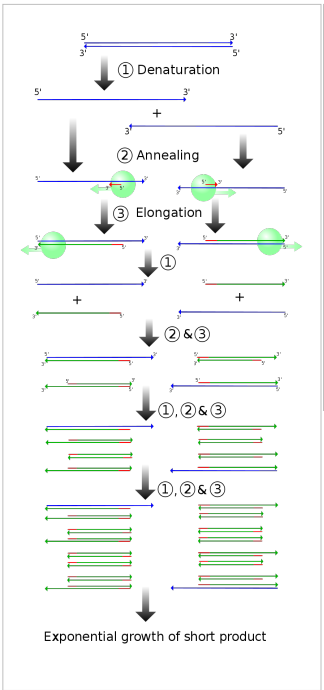

Key:
Telomere
Centromere

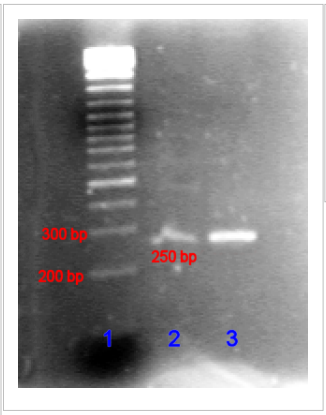

Zytoplasma
DNA
Transkription
Nucleus
mRNA
Translation
Protein
tRNA
mRNA
Ribosom
(rRNA/Protein-Komplex)
Zellmembran

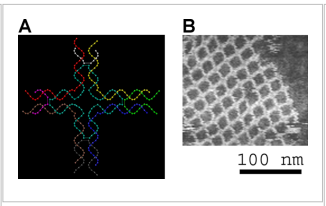

Ende
Beginn
DNA

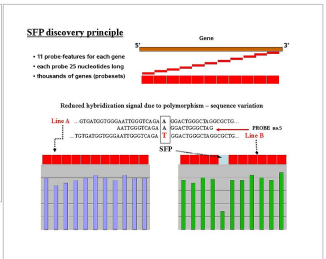

Cross-link DNA
Restriction Digest
Intramolecular Ligation
Reverse Cross-link
Method Specific Processing
3C
4C
5C
Product Quantitation

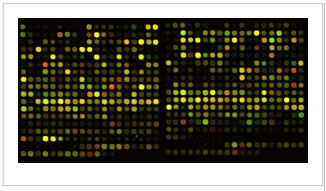

Parkinson
Parkinson
Distonia
MELAS
Distonia
Atassia
Corea
MND
MERRF

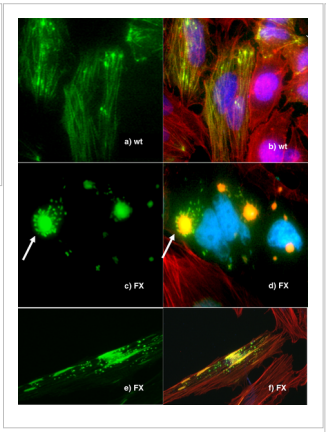


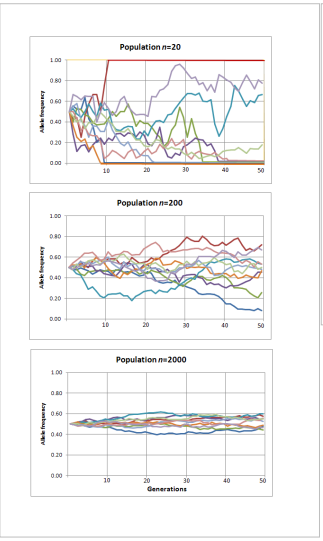












Databases for DNA molecular models and sequences

X-ray diffraction

- NDB ID: UD0017 Database [19]
- X-ray Atlas -database [20]
- PDB files of coordinates for nucleic acid structures from X-ray diffraction by NA (incl. DNA) crystals [21]
- Structure factors dowloadable files in CIF format [22]

Neutron scattering

- ISIS neutron source
- ISIS pulsed neutron source:A world centre for science with neutrons & muons at Harwell, near Oxford, UK. [23]

X-ray microscopy

- Application of X-ray microscopy in the analysis of living hydrated cells [24]

Electron microscopy

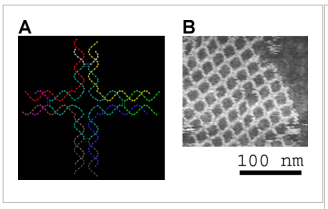
- DNA under electron microscope [25]

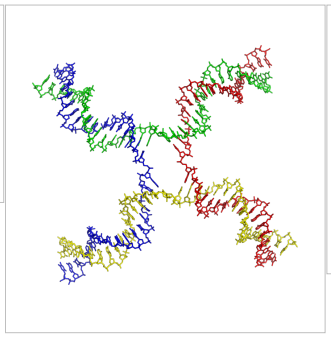
Atomic Force Microscopy (AFM)

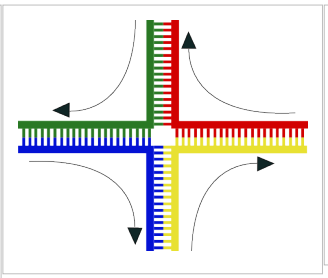
Two-dimensional DNA junction arrays have been visualized by Atomic Force Microscopy (AFM)[26] . Other imaging resources for AFM/Scanning probe microscopy(SPM) can be freely accessed at:

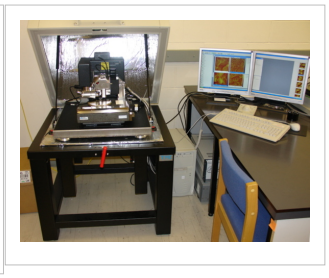
- How SPM Works [27]
- SPM Image Gallery - AFM STM SEM MFM NSOM and more. [28]

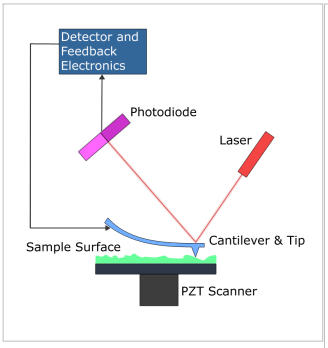
Gallery of AFM Images

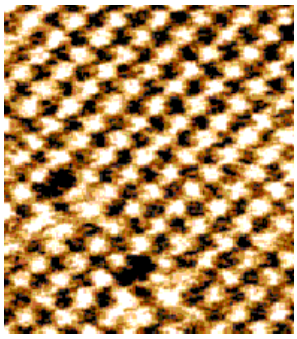


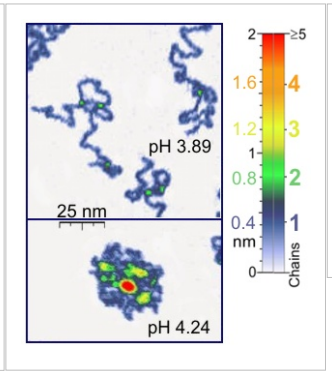


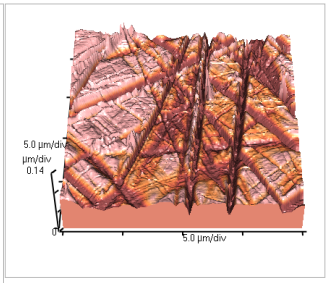




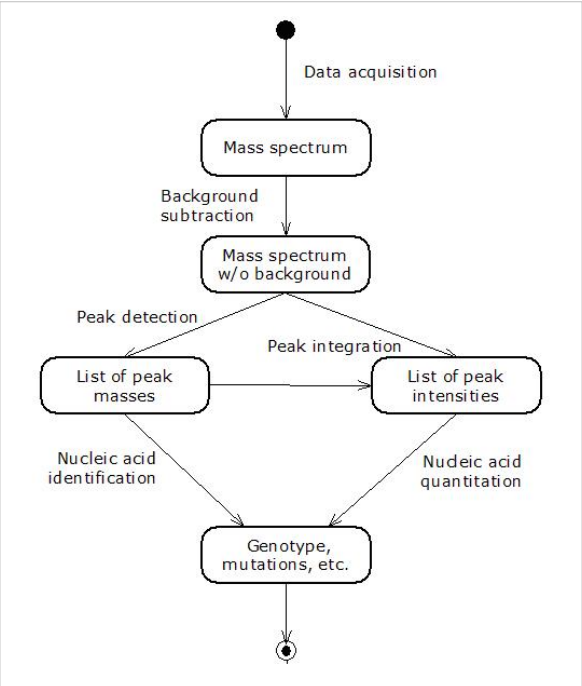








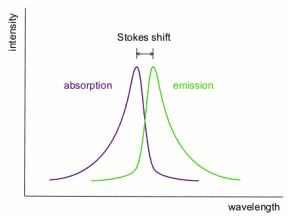
Mass spectrometry--Maldi informatics

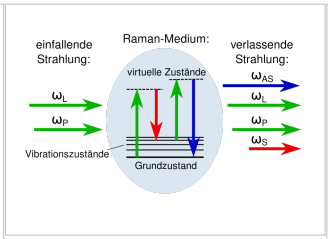


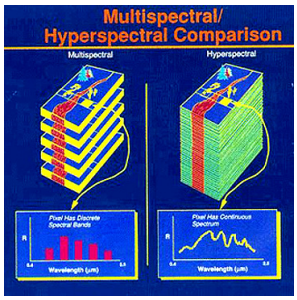
Spectroscopy

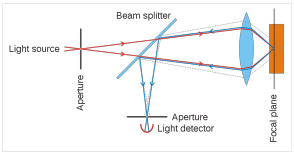
- → Vibrational circular dichroism (VCD)
- FT-NMR[29] [30]
  - NMR Atlas--database [31]
  - mmcif downloadable coordinate files of nucleic acids in solution from 2D-FT NMR data [32]
  - NMR constraints files for NAs in PDB format [33]
- NMR microscopy[34]
- Microwave spectroscopy
- FT-IR
- FT-NIR[35] [36] [37]
- Spectral, Hyperspectral, and → Chemical imaging)[38] [39] [40] [41] [42] [43] [44] .
- Raman spectroscopy/microscopy[45] and CARS[46] .
- Fluorescence correlation spectroscopy[47] [48] [49] [50] [51] [52] [53] [54] , Fluorescence cross-correlation spectroscopy and FRET[55] [56] [57] .
- Confocal microscopy[58]

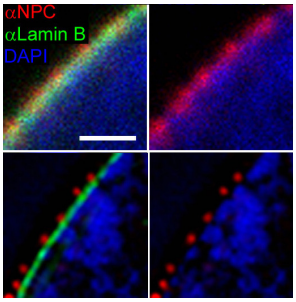
Gallery: CARS (Raman spectroscopy), Fluorescence confocal microscopy, and Hyperspectral imaging

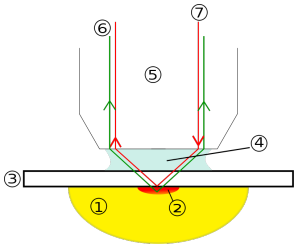


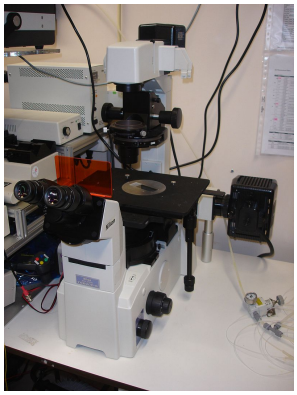


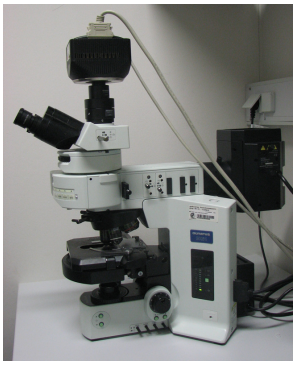


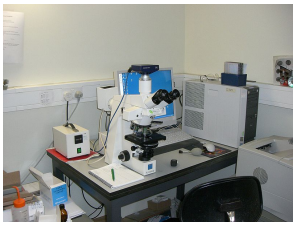


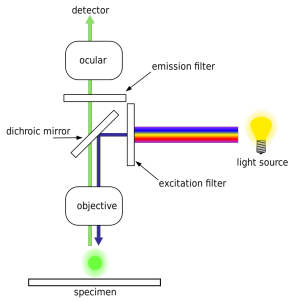


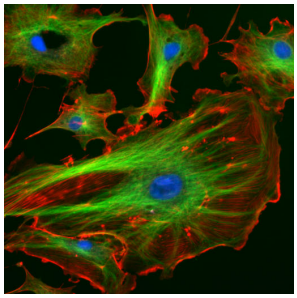


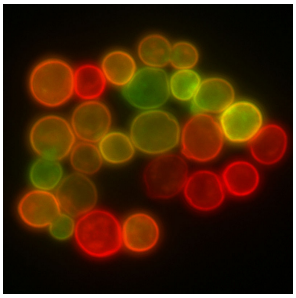


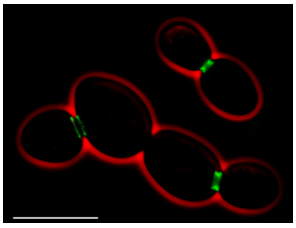


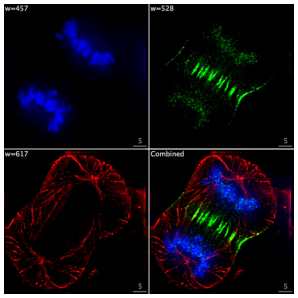


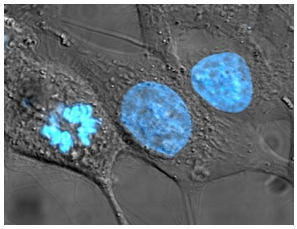


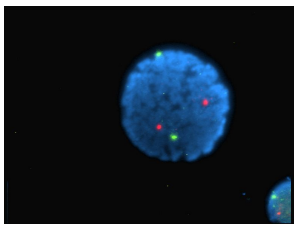
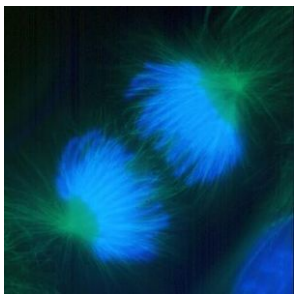
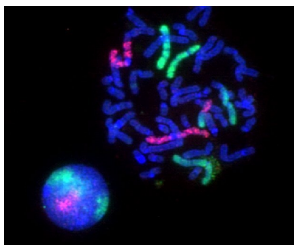
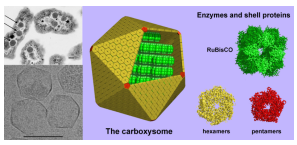










Genomic and structural databases

- CBS Genome Atlas Database [59] — contains examples of base skews.[60]
- The Z curve database of genomes — a 3-dimensional visualization and analysis tool of genomes [61][62] .
- DNA and other nucleic acids' molecular models: Coordinate files of nucleic acids molecular structure models in PDB and CIF formats [63]

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See also

- → DNA
- Molecular graphics
- DNA structure
- → DNA Dynamics
- X-ray scattering
- Neutron scattering
- Crystallography
- Crystal lattices
- → Paracrystalline lattices/Paracrystals
- → 2D-FT NMRI and Spectroscopy
- NMR Spectroscopy
- Microwave spectroscopy
- Two-dimensional IR spectroscopy
- Spectral imaging
- Hyperspectral imaging
- → Chemical imaging
- NMR microscopy
- → VCD or Vibrational circular dichroism
- FRET and FCS- Fluorescence correlation spectroscopy
- Fluorescence cross-correlation spectroscopy (FCCS)
- Molecular structure
- Molecular geometry
- → Molecular topology
- DNA topology
- Sirius visualization software
- Nanostructure
- DNA nanotechnology
- Imaging
- Atomic force microscopy
- X-ray microscopy
- Liquid crystal
- Glasses
- QMC@Home
- Sir Lawrence Bragg, FRS
- Sir John Randall
- James Watson
- Francis Crick
- Maurice Wilkins
- Herbert Wilson, FRS
- Alex Stokes

External links

- DNA the Double Helix Game (http://nobelprize.org/educational_games/medicine/dna_double_helix/) From the official Nobel Prize web site
- MDDNA: Structural Bioinformatics of DNA (http://humphry.chem.wesleyan.edu:8080/MDDNA/)
- Double Helix 1953–2003 (http://www.ncbe.reading.ac.uk/DNA50/) National Centre for Biotechnology Education
- DNA under electron microscope (http://www.fidelitysystems.com/Unlinked_DNA.html)
- Ascalaph DNA (http://www.agilemolecule.com/Ascalaph/Ascalaph_DNA.html) — Commercial software for DNA modeling
- DNAlive: a web interface to compute DNA physical properties (http://mmb.pcb.ub.es/DNAlive). Also allows cross-linking of the results with the UCSC Genome browser and DNA dynamics.
- DiProDB: Dinucleotide Property Database (http://diprodb.fli-leibniz.de). The database is designed to collect and analyse thermodynamic, structural and other dinucleotide properties.
- Further details of mathematical and molecular analysis of DNA structure based on X-ray data (http://planetphysics.org/encyclopedia/BesselFunctionsApplicationsToDiffractionByHelicalStructures.html)
- Bessel functions corresponding to Fourier transforms of atomic or molecular helices. (http://planetphysics.org/?op=getobj&from=objects&name=BesselFunctionsAndTheirApplicationsToDiffractionByHelicalStructures)
- Application of X-ray microscopy in analysis of living hydrated cells (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12379938)
- Characterization in nanotechnology some pdfs (http://nanocharacterization.sitesled.com/)
- overview of STM/AFM/SNOM principles with educative videos (http://www.ntmdt.ru/SPM-Techniques/Principles/)
- SPM Image Gallery - AFM STM SEM MFM NSOM and More (http://www.rhk-tech.com/results/showcase.php)
- How SPM Works (http://www.parkafm.com/New_html/resources/01general.php)
- U.S. National DNA Day (http://www.genome.gov/10506367) — watch videos and participate in real-time discusssions with scientists.
- The Secret Life of DNA - DNA Music compositions (http://www.tjmitchell.com/stuart/dna.html)

Molecular dynamics

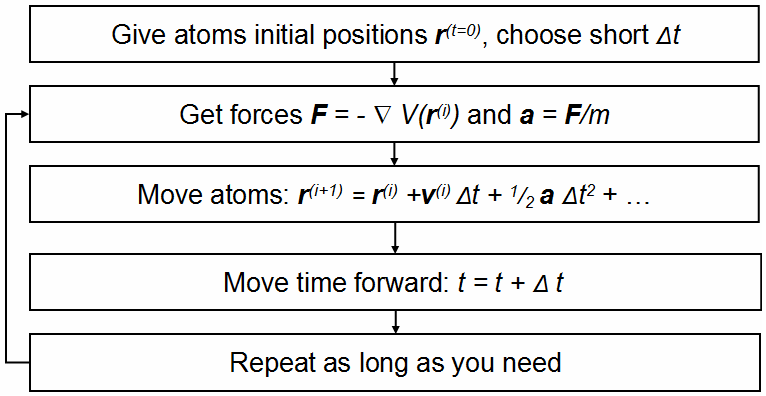
Molecular dynamics (**MD**) is a form of computer simulation in which atoms and molecules are allowed to interact for a period of time by approximations of known physics, giving a view of the motion of the atoms. Because molecular systems generally consist of a vast number of particles, it is impossible to find the properties of such complex systems analytically. When the number of bodies are more than two no analytical solutions can be found and result in chaotic motion (see n-body problem). MD simulation circumvents this problem by using numerical methods. It represents an interface between laboratory experiments and theory, and can be understood as a "virtual experiment". MD probes the relationship between molecular structure, movement and function. Molecular dynamics is a multidisciplinary method. Its laws and theories stem from mathematics, physics, and chemistry, and it employs algorithms from computer science and information theory. It was originally conceived within theoretical physics in the late 1950s[1] and early 1960s [2] , but is applied today mostly in materials science and modeling of biomolecules.

Before it became possible to simulate molecular dynamics with computers, some undertook the hard work of trying it with physical models such as macroscopic spheres. The idea was to arrange them to replicate the properties of a liquid. J.D. Bernal said, in 1962: "... I took a number of rubber balls and stuck them together with rods of a selection of different lengths ranging from 2.75 to 4 inches. I tried to do this in the first place as casually as possible, working in my own office, being interrupted every five minutes or so and not remembering what I had done before the interruption."[3] Fortunately, now computers keep track of bonds during a simulation.

Molecular dynamics is a specialized discipline of molecular modeling and computer simulation based on statistical mechanics; the main justification of the MD method is that statistical ensemble averages are equal to time averages of the system, known as the ergodic hypothesis. MD has also been termed "statistical mechanics by numbers" and "Laplace's vision of Newtonian mechanics" of predicting the future by animating nature's forces[4] [5] and allowing insight into molecular motion on an atomic scale. However, long MD simulations are mathematically ill-conditioned, generating cumulative errors in numerical integration that can be minimized with proper selection of algorithms and parameters, but not eliminated entirely. Furthermore, current potential functions are, in many cases, not sufficiently accurate to reproduce the dynamics of molecular systems, so the much more computationally demanding Ab Initio Molecular Dynamics method must be used. Nevertheless, molecular dynamics techniques allow detailed time and space resolution into representative behavior in phase space.

Areas of Application

There is a significant difference between the focus and methods used by chemists and physicists, and this is reflected in differences in the jargon used by the different fields. In chemistry and biophysics, the interaction between the particles is either described by a "force field" (**classical MD**), a quantum chemical model, or a mix between the two. These terms are not used in physics, where the interactions are usually described by the name of the theory or approximation being used and called the potential energy, or just "potential".



Highly simplified description of the molecular dynamics simulation algorithm. The simulation proceeds iteratively by alternatively calculating forces and solving the equations of motion based on the accelerations obtained from the new forces. In practise, almost all MD codes use much more complicated versions of the algorithm, including two steps (predictor and corrector) in solving the equations of motion and many additional steps for e.g. temperature and pressure control, analysis and output.

Beginning in theoretical physics, the method of MD gained popularity in materials science and since the 1970s also in biochemistry and biophysics. In chemistry, MD serves as an important tool in protein structure determination and refinement using experimental tools such as X-ray crystallography and NMR. It has also been applied with limited success as a method of refining protein structure predictions. In physics, MD is used to examine the dynamics of atomic-level phenomena that cannot be observed directly, such as thin film growth and ion-subplantation. It is also used to examine the physical properties of nanotechnological devices that have not or cannot yet be created.

In applied mathematics and theoretical physics, molecular dynamics is a part of the research realm of dynamical systems, ergodic theory and statistical mechanics in general. The concepts of energy conservation and molecular entropy come from thermodynamics. Some techniques to calculate conformational entropy such as principal components analysis come from information theory. Mathematical techniques such as the transfer operator become applicable when MD is seen as a Markov chain. Also, there is a large community of mathematicians working on volume preserving, symplectic integrators for more computationally efficient MD simulations.

MD can also be seen as a special case of the discrete element method (DEM) in which the particles have spherical shape (e.g. with the size of their van der Waals radii.) Some authors in the DEM community employ the term MD rather loosely, even when their simulations do not model actual molecules.

Design Constraints

Design of a molecular dynamics simulation should account for the available computational power. Simulation size (n=number of particles), timestep and total time duration must be selected so that the calculation can finish within a reasonable time period. However, the simulations should be long enough to be relevant to the time scales of the natural processes being studied. To make statistically valid conclusions from the simulations, the time span simulated should match the kinetics of the natural process. Otherwise, it is analogous to making conclusions about how a human walks from less than one footstep. Most scientific publications about the dynamics of proteins and DNA use data from simulations spanning nanoseconds (1E-9 s) to microseconds (1E-6 s). To obtain these simulations, several CPU-days to CPU-years are needed. Parallel algorithms allow the load to be distributed among CPUs; an example is the spatial decomposition in LAMMPS.

During a classical MD simulation, the most CPU intensive task is the evaluation of the potential (force field) as a function of the particles' internal coordinates. Within that energy evaluation, the most expensive one is the non-bonded or non-covalent part. In Big O notation, common molecular dynamics simulations scale by $O(n^2)$ if all pair-wise electrostatic and van der Waals interactions must be accounted for explicitly. This computational cost can be reduced by employing electrostatics methods such as Particle Mesh Ewald ($O(n\log(n))$) or good spherical cutoff techniques ($O(n)$).

Another factor that impacts total CPU time required by a simulation is the size of the integration timestep. This is the time length between evaluations of the potential. The timestep must be chosen small enough to avoid discretization errors (i.e. smaller than the fastest vibrational frequency in the system). Typical timesteps for classical MD are in the order of 1 femtosecond (1E-15 s). This value may be extended by using algorithms such as SHAKE, which fix the vibrations of the fastest atoms (e.g. hydrogens) into place. Multiple time scale methods have also been developed, which allow for extended times between updates of slower long-range forces.[6] [7] [8]

For simulating molecules in a solvent, a choice should be made between explicit solvent and implicit solvent. Explicit solvent particles (such as the TIP3P and SPC/E water models) must be calculated expensively by the force field, while implicit solvents use a mean-field approach. Using an explicit solvent is computationally expensive, requiring inclusion of about ten times more particles in the simulation. But the granularity and viscosity of explicit solvent is essential to reproduce certain properties of the solute molecules. This is especially important to reproduce kinetics.

In all kinds of molecular dynamics simulations, the simulation box size must be large enough to avoid boundary condition artifacts. Boundary conditions are often treated by choosing fixed values at the edges, or by employing periodic boundary conditions in which one side of the simulation loops back to the opposite side, mimicking a bulk phase.

Microcanonical ensemble (NVE)

In the **microcanonical**, or **NVE** ensemble, the system is isolated from changes in moles (N), volume (V) and energy (E). It corresponds to an adiabatic process with no heat exchange. A microcanonical molecular dynamics trajectory may be seen as an exchange of potential and kinetic energy, with total energy being conserved. For a system of N particles with coordinates X and velocities V, the following pair of first order differential equations may be written in Newton's notation as

$$F(X) = -\nabla U(X) = M\dot{V}(t)$$
$$V(t) = \dot{X}(t).$$

The potential energy function $U(X)$ of the system is a function of the particle coordinates X. It is referred to simply as the "potential" in Physics, or the "force field" in Chemistry. The first equation comes from Newton's laws; the force F acting on each particle in the system can be calculated as the negative gradient of $U(X)$.

For every timestep, each particle's position X and velocity V may be integrated with a symplectic method such as Verlet. The time evolution of X and V is called a trajectory. Given the initial positions (e.g. from theoretical knowledge) and velocities (e.g. randomized Gaussian), we can calculate all future (or past) positions and velocities.

One frequent source of confusion is the meaning of temperature in MD. Commonly we have experience with macroscopic temperatures, which involve a huge number of particles. But temperature is a statistical quantity. If there is a large enough number of atoms, statistical temperature can be estimated from the *instantaneous temperature*, which is found by equating the kinetic energy of the system to $nk_BT/2$ where n is the number of degrees of freedom of the system.

A temperature-related phenomenon arises due to the small number of atoms that are used in MD simulations. For example, consider simulating the growth of a copper film starting with a substrate containing 500 atoms and a deposition energy of 100 eV. In the real world, the 100 eV from the deposited atom would rapidly be transported through and shared among a large number of atoms (10^{10} or more) with no big change in temperature. When there are only 500 atoms, however, the substrate is almost immediately vaporized by the deposition. Something similar happens in biophysical simulations. The temperature of the system in NVE is naturally raised when macromolecules such as proteins undergo exothermic conformational changes and binding.

Canonical ensemble (NVT)

In the canonical ensemble, moles (N), volume (V) and temperature (T) are conserved. It is also sometimes called constant temperature molecular dynamics (CTMD). In NVT, the energy of endothermic and exothermic processes is exchanged with a thermostat.

A variety of thermostat methods are available to add and remove energy from the boundaries of an MD system in a realistic way, approximating the canonical ensemble. Popular techniques to control temperature include the Nosé-Hoover thermostat, the Berendsen thermostat, and Langevin dynamics. Note that the Berendsen thermostat might introduce the flying ice cube effect, which leads to unphysical translations and rotations of the simulated system.

Isothermal-Isobaric (NPT) ensemble

In the isothermal-isobaric ensemble, moles (N), pressure (P) and temperature (T) are conserved. In addition to a thermostat, a barostat is needed. It corresponds most closely to laboratory conditions with a flask open to ambient temperature and pressure.

In the simulation of biological membranes, isotropic pressure control is not appropriate. For lipid bilayers, pressure control occurs under constant membrane area (NPAT) or constant surface tension "gamma" (NPγT).

Generalized ensembles

The replica exchange method is a generalized ensemble. It was originally created to deal with the slow dynamics of disordered spin systems. It is also called parallel tempering. The replica exchange MD (REMD) formulation [9] tries to overcome the multiple-minima problem by exchanging the temperature of non-interacting replicas of the system running at several temperatures.

Potentials in MD simulations

A molecular dynamics simulation requires the definition of a potential function, or a description of the terms by which the particles in the simulation will interact. In chemistry and biology this is usually referred to as a force field. Potentials may be defined at many levels of physical accuracy; those most commonly used in chemistry are based on molecular mechanics and embody a classical treatment of particle-particle interactions that can reproduce structural and conformational changes but usually cannot reproduce chemical reactions.

The reduction from a fully quantum description to a classical potential entails two main approximations. The first one is the Born-Oppenheimer approximation, which states that the dynamics of electrons is so fast that they can be considered to react instantaneously to the motion of their nuclei. As a consequence, they may be treated separately. The second one treats the nuclei, which are much heavier than electrons, as point particles that follow classical Newtonian dynamics. In classical molecular dynamics the effect of the electrons is approximated as a single potential energy surface, usually representing the ground state.

When finer levels of detail are required, potentials based on quantum mechanics are used; some techniques attempt to create hybrid classical/quantum potentials where the bulk of the system is treated classically but a small region is treated as a quantum system, usually undergoing a chemical transformation.

Empirical potentials

Empirical potentials used in chemistry are frequently called force fields, while those used in materials physics are called just empirical or analytical potentials.

Most force fields in chemistry are empirical and consist of a summation of bonded forces associated with chemical bonds, bond angles, and bond dihedrals, and non-bonded forces associated with van der Waals forces and electrostatic charge. Empirical potentials represent quantum-mechanical effects in a limited way through ad-hoc functional approximations. These potentials contain free parameters such as atomic charge, van der Waals parameters reflecting estimates of atomic radius, and equilibrium bond length, angle, and dihedral; these are obtained by fitting against detailed electronic calculations

(quantum chemical simulations) or experimental physical properties such as elastic constants, lattice parameters and spectroscopic measurements.

Because of the non-local nature of non-bonded interactions, they involve at least weak interactions between all particles in the system. Its calculation is normally the bottleneck in the speed of MD simulations. To lower the computational cost, force fields employ numerical approximations such as shifted cutoff radii, reaction field algorithms, particle mesh Ewald summation, or the newer Particle-Particle Particle Mesh (P3M).

Chemistry force fields commonly employ preset bonding arrangements (an exception being *ab-initio* dynamics), and thus are unable to model the process of chemical bond breaking and reactions explicitly. On the other hand, many of the potentials used in physics, such as those based on the bond order formalism can describe several different coordinations of a system and bond breaking. Examples of such potentials include the Brenner potential[10] for hydrocarbons and its further developments for the C-Si-H and C-O-H systems. The ReaxFF potential[11] can be considered a fully reactive hybrid between bond order potentials and chemistry force fields.

Pair potentials vs.many-body potentials

The potential functions representing the non-bonded energy are formulated as a sum over interactions between the particles of the system. The simplest choice, employed in many popular force fields, is the "pair potential", in which the total potential energy can be calculated from the sum of energy contributions between pairs of atoms. An example of such a pair potential is the non-bonded Lennard-Jones potential (also known as the 6-12 potential), used for calculating van der Waals forces.

$$U(r) = 4\varepsilon \left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6} \right]$$

Another example is the Born (ionic) model of the ionic lattice. The first term in the next equation is Coulomb's law for a pair of ions, the second term is the short-range repulsion explained by Pauli's exclusion principle and the final term is the dispersion interaction term. Usually, a simulation only includes the dipolar term, although sometimes the quadrupolar term is included as well.

$$U_{ij}(r_{ij}) = \sum \frac{z_i z_j}{4\pi\epsilon_0} \frac{1}{r_{ij}} + \sum A_l \exp \frac{-r_{ij}}{p_l} + \sum C_l r_{ij}^{-n_j} + \cdots$$

In many-body potentials, the potential energy includes the effects of three or more particles interacting with each other. In simulations with pairwise potentials, global interactions in the system also exist, but they occur only through pairwise terms. In many-body potentials, the potential energy cannot be found by a sum over pairs of atoms, as these interactions are calculated explicitly as a combination of higher-order terms. In the statistical view, the dependency between the variables cannot in general be expressed using only pairwise products of the degrees of freedom. For example, the Tersoff potential[12] , which was originally used to simulate carbon, silicon and germanium and has since been used for a wide range of other materials, involves a sum over groups of three atoms, with the angles between the atoms being an important factor in the potential. Other examples are the embedded-atom method (EAM)[13] and the Tight-Binding Second Moment Approximation (TBSMA) potentials[14] , where the electron density of states in the region of an atom is calculated from a sum of contributions from surrounding atoms, and the potential energy contribution is then a function of this sum.

Semi-empirical potentials

Semi-empirical potentials make use of the matrix representation from quantum mechanics. However, the values of the matrix elements are found through empirical formulae that estimate the degree of overlap of specific atomic orbitals. The matrix is then diagonalized to determine the occupancy of the different atomic orbitals, and empirical formulae are used once again to determine the energy contributions of the orbitals.

There are a wide variety of semi-empirical potentials, known as tight-binding potentials, which vary according to the atoms being modeled.

Polarizable potentials

Most classical force fields implicitly include the effect of polarizability, e.g. by scaling up the partial charges obtained from quantum chemical calculations. These partial charges are stationary with respect to the mass of the atom. But molecular dynamics simulations can explicitly model polarizability with the introduction of induced dipoles through different methods, such as Drude particles or fluctuating charges. This allows for a dynamic redistribution of charge between atoms which responds to the local chemical environment.

For many years, polarizable MD simulations have been touted as the next generation. For homogenous liquids such as water, increased accuracy has been achieved through the inclusion of polarizability.[15] Some promising results have also been achieved for proteins.[16] However, it is still uncertain how to best approximate polarizability in a simulation.

Ab-initio methods

In classical molecular dynamics, a single potential energy surface (usually the ground state) is represented in the force field. This is a consequence of the Born-Oppenheimer approximation. If excited states, chemical reactions or a more accurate representation is needed, electronic behavior can be obtained from first principles by using a quantum mechanical method, such as Density Functional Theory. This is known as Ab Initio Molecular Dynamics (AIMD). Due to the cost of treating the electronic degrees of freedom, the computational cost of this simulations is much higher than classical molecular dynamics. This implies that AIMD is limited to smaller systems and shorter periods of time.

Ab-initio quantum-mechanical methods may be used to calculate the potential energy of a system on the fly, as needed for conformations in a trajectory. This calculation is usually made in the close neighborhood of the reaction coordinate. Although various approximations may be used, these are based on theoretical considerations, not on empirical fitting. *Ab-Initio* calculations produce a vast amount of information that is not available from empirical methods, such as density of electronic states or other electronic properties. A significant advantage of using *ab-initio* methods is the ability to study reactions that involve breaking or formation of covalent bonds, which correspond to multiple electronic states.

A popular software for *ab-initio* molecular dynamics is the Car-Parrinello Molecular Dynamics (CPMD) package based on the density functional theory.

Hybrid QM/MM

QM (quantum-mechanical) methods are very powerful. However, they are computationally expensive, while the MM (classical or molecular mechanics) methods are fast but suffer from several limitations (require extensive parameterization; energy estimates obtained are not very accurate; cannot be used to simulate reactions where covalent bonds are broken/formed; and are limited in their abilities for providing accurate details regarding the chemical environment). A new class of method has emerged that combines the good points of QM (accuracy) and MM (speed) calculations. These methods are known as mixed or hybrid quantum-mechanical and molecular mechanics methods (hybrid QM/MM). The methodology for such techniques was introduced by Warshel and coworkers. In the recent years have been pioneered by several groups including: Arieh Warshel (University of Southern California), Weitao Yang (Duke University), Sharon Hammes-Schiffer (The Pennsylvania State University), Donald Truhlar and Jiali Gao (University of Minnesota) and Kenneth Merz (University of Florida).

The most important advantage of hybrid QM/MM methods is the speed. The cost of doing classical molecular dynamics (MM) in the most straightforward case scales $O(n^2)$, where N is the number of atoms in the system. This is mainly due to electrostatic interactions term (every particle interacts with every other particle). However, use of cutoff radius, periodic pair-list updates and more recently the variations of the particle-mesh Ewald's (PME) method has reduced this between O(N) to $O(n^2)$. In other words, if a system with twice many atoms is simulated then it would take between twice to four times as much computing power. On the other hand the simplest *ab-initio* calculations typically scale $O(n^3)$ or worse (Restricted Hartree-Fock calculations have been suggested to scale $\sim O(n^{2.7})$). To overcome the limitation, a small part of the system is treated quantum-mechanically (typically active-site of an enzyme) and the remaining system is treated classically.

In more sophisticated implementations, QM/MM methods exist to treat both light nuclei susceptible to quantum effects (such as hydrogens) and electronic states. This allows generation of hydrogen wave-functions (similar to electronic wave-functions). This methodology has been useful in investigating phenomenon such as hydrogen tunneling. One example where QM/MM methods have provided new discoveries is the calculation of hydride transfer in the enzyme liver alcohol dehydrogenase. In this case, tunneling is important for the hydrogen, as it determines the reaction rate.[17]

Coarse-graining and reduced representations

At the other end of the detail scale are coarse-grained and lattice models. Instead of explicitly representing every atom of the system, one uses "pseudo-atoms" to represent groups of atoms. MD simulations on very large systems may require such large computer resources that they cannot easily be studied by traditional all-atom methods. Similarly, simulations of processes on long timescales (beyond about 1 microsecond) are prohibitively expensive, because they require so many timesteps. In these cases, one can sometimes tackle the problem by using reduced representations, which are also called coarse-grained models.

Examples for coarse graining (CG) methods are discontinuous molecular dynamics (CG-DMD)[18] [19] and Go-models[20] . Coarse-graining is done sometimes taking larger pseudo-atoms. Such united atom approximations have been used in MD simulations of biological membranes. The aliphatic tails of lipids are represented by a few pseudo-atoms

by gathering 2-4 methylene groups into each pseudo-atom.

The parameterization of these very coarse-grained models must be done empirically, by matching the behavior of the model to appropriate experimental data or all-atom simulations. Ideally, these parameters should account for both enthalpic and entropic contributions to free energy in an implicit way. When coarse-graining is done at higher levels, the accuracy of the dynamic description may be less reliable. But very coarse-grained models have been used successfully to examine a wide range of questions in structural biology.

Examples of applications of coarse-graining in biophysics:

- protein folding studies are often carried out using a single (or a few) pseudo-atoms per amino acid;
- DNA supercoiling has been investigated using 1-3 pseudo-atoms per basepair, and at even lower resolution;
- Packaging of → double-helical DNA into bacteriophage has been investigated with models where one pseudo-atom represents one turn (about 10 basepairs) of the double helix;
- RNA structure in the ribosome and other large systems has been modeled with one pseudo-atom per nucleotide.

The simplest form of coarse-graining is the "united atom" (sometimes called "extended atom") and was used in most early MD simulations of proteins, lipids and nucleic acids. For example, instead of treating all four atoms of a CH_3 methyl group explicitly (or all three atoms of CH_2 methylene group), one represents the whole group with a single pseudo-atom. This pseudo-atom must, of course, be properly parameterized so that its van der Waals interactions with other groups have the proper distance-dependence. Similar considerations apply to the bonds, angles, and torsions in which the pseudo-atom participates. In this kind of united atom representation, one typically eliminates all explicit hydrogen atoms except those that have the capability to participate in hydrogen bonds ("polar hydrogens"). An example of this is the Charmm 19 force-field.

The polar hydrogens are usually retained in the model, because proper treatment of hydrogen bonds requires a reasonably accurate description of the directionality and the electrostatic interactions between the donor and acceptor groups. A hydroxyl group, for example, can be both a hydrogen bond donor and a hydrogen bond acceptor, and it would be impossible to treat this with a single OH pseudo-atom. Note that about half the atoms in a protein or nucleic acid are nonpolar hydrogens, so the use of united atoms can provide a substantial savings in computer time.

Examples of applications

Molecular dynamics is used in many fields of science.

- First macromolecular MD simulation published (1977, Size: 500 atoms, Simulation Time: 9.2 ps=0.0092 ns, Program: CHARMM precursor) Protein: Bovine Pancreatic Trypsine Inhibitor. This is one of the best studied proteins in terms of folding and kinetics. Its simulation published in Nature magazine paved the way for understanding protein motion as essential in function and not just accessory.[21]
- MD is the standard method to treat collision cascades in the heat spike regime, i.e. the effects that energetic neutron and ion irradiation have on solids an solid surfaces.[22] [23]

The following two biophysical examples are not run-of-the-mill MD simulations. They illustrate almost heroic efforts to produce simulations of a system of very large size (a complete virus) and very long simulation times (500 microseconds):

- MD simulation of the complete satellite tobacco mosaic virus (**STMV**) (2006, Size: 1 million atoms, Simulation time: 50 ns, program: NAMD) This virus is a small, icosahedral plant virus which worsens the symptoms of infection by Tobacco Mosaic Virus (TMV). Molecular dynamics simulations were used to probe the mechanisms of viral assembly. The entire STMV particle consists of 60 identical copies of a single protein that make up the viral capsid (coating), and a 1063 nucleotide single stranded RNA genome. One key finding is that the capsid is very unstable when there is no RNA inside. The simulation would take a single 2006 desktop computer around 35 years to complete. It was thus done in many processors in parallel with continuous communication between them.[24]
- Folding Simulations of the Villin Headpiece in All-Atom Detail (2006, Size: 20,000 atoms; Simulation time: 500 μs = 500,000 ns, Program: folding@home) This simulation was run in 200,000 CPU's of participating personal computers around the world. These computers had the folding@home program installed, a large-scale distributed computing effort coordinated by Vijay Pande at Stanford University. The kinetic properties of the Villin Headpiece protein were probed by using many independent, short trajectories run by CPU's without continuous real-time communication. One technique employed was the Pfold value analysis, which measures the probability of folding before unfolding of a specific starting conformation. Pfold gives information about transition state structures and an ordering of conformations along the folding pathway. Each trajectory in a Pfold calculation can be relatively short, but many independent trajectories are needed.[25]

Molecular dynamics algorithms

Integrators

- Verlet integration
- Beeman's algorithm
- Gear predictor - corrector
- Constraint algorithms (for constrained systems)
- Symplectic integrator

Short-range interaction algorithms

- Cell lists
- Verlet list
- Bonded interactions

Long-range interaction algorithms

- Ewald summation
- Particle Mesh Ewald (PME)
- Particle-Particle Particle Mesh P3M
- Reaction Field Method

Parallelization strategies

- Domain decomposition method (Distribution of system data for parallel computing)
- Molecular Dynamics - Parallel Algorithms [26]

Major software for MD simulations

- Abalone (classical, implicit water)
- ABINIT (DFT)
- ADUN [27] (classical, P2P database for simulations)
- AMBER (classical)
- Ascalaph [28] (classical, GPU accelerated)
- CASTEP (DFT)
- CPMD (DFT)
- CP2K [29] (DFT)
- CHARMM (classical, the pioneer in MD simulation, extensive analysis tools)
- COSMOS [30] (classical and hybrid QM/MM, quantum-mechanical atomic charges with BPT)
- Desmond [31] (classical, parallelization with up to thousands of CPU's)
- DL_POLY [32] (classical)
- ESPResSo (classical, coarse-grained, parallel, extensible)
- Fireball [33] (tight-binding DFT)
- GROMACS (classical)
- GROMOS (classical)
- GULP (classical)
- Hippo [34] (classical)
- LAMMPS (classical, large-scale with spatial-decomposition of simulation domain for parallelism)
- MDynaMix (classical, parallel)
- MOLDY [35] (classical, parallel) latest release [36]
- Materials Studio [37] (Forcite MD using COMPASS, Dreiding, Universal, cvff and pcff forcefields in serial or parallel, QMERA (QM+MD), ONESTEP (DFT), etc.)
- MOSCITO (classical)
- NAMD (classical, parallelization with up to thousands of CPU's)
- NEWTON-X [38] (ab initio, surface-hopping dynamics)
- ProtoMol [39] (classical, extensible, includes multigrid electrostatics)
- PWscf (DFT)
- S/PHI/nX [40] (DFT)
- SIESTA (DFT)
- VASP (DFT)
- TINKER (classical)
- YASARA [41] (classical)
- ORAC [42] (classical)
- XMD (classical)

Related software

- VMD - MD simulation trajectories can be visualized and analyzed.
- PyMol - Molecular Visualization software written in python
- Packmol [43] Package for building starting configurations for MD in an automated fashion
- Sirius - Molecular modeling, analysis and visualization of MD trajectories
- esra [44] - Lightweight molecular modeling and analysis library (Java/Jython/Mathematica).
- Molecular Workbench [45] - Interactive molecular dynamics simulations on your desktop
- BOSS - MC in OPLS

Specialized hardware for MD simulations

- Anton - A specialized, massively parallel supercomputer designed to execute MD simulations.
- MDGRAPE - A special purpose system built for molecular dynamics simulations, especially protein structure prediction.

See also

- Molecular modeling
- Computational chemistry
- Energy drift
- Force field in Chemistry
- Force field implementation
- Monte Carlo method
- Molecular Design software
- Molecular mechanics
- Molecular modeling on GPU
- Protein dynamics
- Implicit solvation
- Car-Parrinello method
- Symplectic numerical integration
- Software for molecular mechanics modeling
- Dynamical systems
- Theoretical chemistry
- Statistical mechanics
- Quantum chemistry
- Discrete element method
- List of nucleic acid simulation software

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- Oren M. Becker, Alexander D. Mackerell Jr, Benoît Roux, Masakatsu Watanabe (2001) Computational Biochemistry and Biophysics. Marcel Dekker. ISBN 0-8247-0455-X.
- Andrew Leach (2001) Molecular Modelling: Principles and Applications. (2nd Edition) Prentice Hall. ISBN 978-0582382107.
- Tamar Schlick (2002) Molecular Modeling and Simulation. Springer. ISBN 0-387-95404-X.
- William Graham Hoover (1991) Computational Statistical Mechanics, Elsevier, ISBN 0-444-88192-1.

External links

- The Blue Gene Project (http://researchweb.watson.ibm.com/bluegene/) (IBM)
- D. E. Shaw Research (http://deshawresearch.com/) (D. E. Shaw Research)
- Molecular Physics (http://www.tandf.co.uk/journals/titles/00268976.asp)
- Statistical mechanics of Nonequilibrium Liquids (http://www.phys.unsw.edu.au/~gary/book.html) Lecture Notes on non-equilibrium MD
- Introductory Lecture on Classical Molecular Dynamics (http://www.fz-juelich.de/nic-series/volume10/sutmann.pdf) by Dr. Godehard Sutmann, NIC, Forschungszentrum Jülich, Germany
- Introductory Lecture on Ab Initio Molecular Dynamics and Ab Initio Path Integrals (http://www.fz-juelich.de/nic-series/volume10/tuckerman2.pdf) by Mark E. Tuckerman, New York University, USA
- Introductory Lecture on Ab initio molecular dynamics: Theory and Implementation (http://www.fz-juelich.de/nic-series/Volume1/marx.pdf) by Dominik Marx, Ruhr-Universität Bochum and Jürg Hutter, Universität Zürich
- Atomic-scale Friction Research and Education Synergy Hub (AFRESH) (http://nsfafresh.org) an Engineering Virtual Organization for the atomic-scale friction community to share, archive, link, and discuss data, knowledge and tools related to atomic-scale friction.
  - AFRESH (http://nsfafresh.org/wiki/index.php?title=Computational_Tribology) also provides detailed information regarding computational methods such as Molecular Dynamics as it relates to atomic-scale friction research.

DNA Dynamics

DNA Molecular dynamics modeling involves simulations of → DNA molecular geometry and topology changes with time as a result of both intra- and inter- molecular interactions of DNA. Whereas molecular models of Deoxyribonucleic acid (→ DNA) molecules such as closely packed spheres (CPK models) made of plastic or metal wires for 'skeletal models' are useful representations of static DNA structures, their usefluness is very limited for representing complex DNA dynamics. Computer molecular modeling allows both animations and molecular dynamics simulations that are very important for understanding how DNA functions *in vivo*.

An old standing dynamic problem is how DNA "self-replication" takes place in living cells that should involve transient uncoiling of supercoiled DNA fibers. Altough DNA consists of relatively rigid, very large elongated biopolymer molecules called "fibers" or chains its molecular stucture *in vivo* undergoes dynamic configuration changes that involve dynamically attached water molecules, ions or proteins/enzymes. Supercoiling, packing with histones in chromosome structures, and other such supramolecular aspects also involve *in vivo* DNA topology which is even more complex than DNA molecular geometry, thus turning molecular modeling of DNA dynamics into a series of challenging problems for biophysical chemists, molecular biologists and biotechnologists. Thus, DNA exists in multiple stable geometries (called conformational isomerism) and has a rather large number of configurational, quantum states which are close to each other in energy on the potential energy surface of the DNA molecule.

Such varying molecular geometries can also be computed, at least in principle, by employing *ab initio* quantum chemistry methods that can attain high accuracy for small molecules, although claims that acceptable accuracy can be also achieved for polynuclelotides, as well as DNA conformations, were recenlty made on the basis of VCD spectral data. Such quantum geometries define an important class of *ab initio* molecular models of DNA whose exploration has barely started especially in connection with results obtained by VCD in solutions. More detailed comparisons with such *ab initio* quantum computations are in principle obtainable through 2D-FT NMR spectroscopy and relaxation studies of polynucleotide solutions or specifically labeled DNA, as for example with deuterium labels.

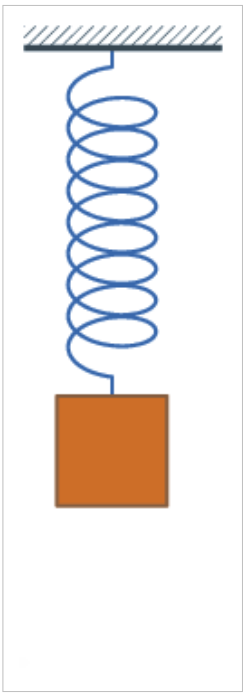
Importance of DNA molecular structure and dynamics modeling for Genomics and beyond

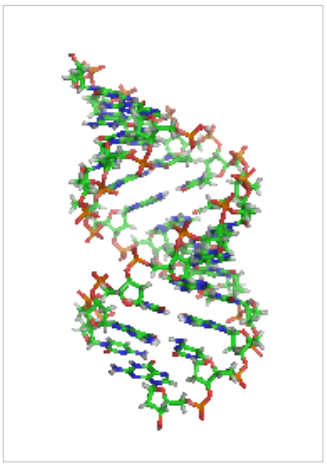
From the very early stages of structural studies of DNA by X-ray diffraction and biochemical means, molecular models such as the Watson-Crick double-helix model were succesfully employed to solve the 'puzzle' of DNA structure, and also find how the latter relates to its key functions in living cells. The first high quality X-ray diffraction patterns of A-DNA were reported by Rosalind Franklin and Raymond Gosling in 1953[1] . The first reports of a double-helix molecular model of B-DNA structure were made by Watson and Crick in 1953[2] [3] . Then Maurice F. Wilkins, A. Stokes and H.R. Wilson, reported the first X-ray patterns of *in vivo* B-DNA in partially oriented salmon sperm heads [6] . The development of the first correct double-helix molecular model of DNA by Crick and Watson may not have been possible without the biochemical evidence for the nucleotide base-pairing ([A---T]; [C---G]), or Chargaff's rules[7] [8] [9] [10] [11] [12] . Although such initial studies of DNA structures with the help of molecular models were essentially static, their consequences for explaining the *in vivo* functions of DNA were significant in the areas of protein biosynthesis and the quasi-universality of the genetic code. Epigenetic transformation studies of DNA *in vivo* were however much slower to develop in spite of their importance for embryology, morphogenesis and cancer research. Such chemical dynamics and biochemical reactions of DNA are much more complex than the molecular dynamics of DNA physical interactions with water, ions and proteins/enzymes in living cells.

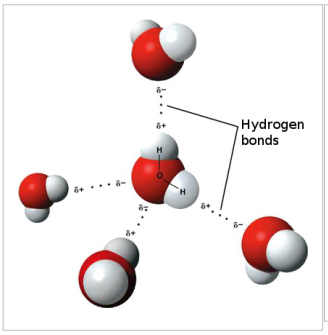
Animated DNA molecular models and hydrogen-bonding

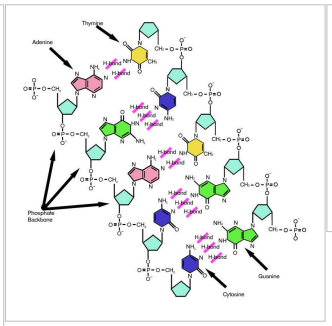
Animated molecular models allow one to visually explore the three-dimensional (3D) structure of DNA. The first DNA model is a space-filling, or CPK, model of the DNA double-helix whereas the third is an animated wire, or skeletal type, molecular model of DNA. The last two DNA molecular models in this series depict quadruplex DNA [4] that may be involved in certain cancers[5] [6] . The first CPK model in the second row is a molecular model of hydrogen bonds between water molecules in ice that are broadly similar to those found in DNA; the hydrogen bonding dynamics and proton exchange is however very different by many orders of magnitude between the two systems of fully hydrated DNA and water molecules in ice. Thus, the DNA dynamics is complex involving nanosecond and several tens of picosecond time scales, whereas that of liquid ice is on the picosecond time scale, and that of proton exchange in ice is on the millisecond time scale; the proton exchange rates in DNA and attached proteins may vary from picosecond to nanosecond, minutes or years, depending on the exact locations of the exchanged protons in the large

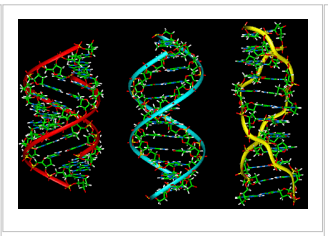
biopolymers. The simple harmonic oscillator 'vibration' in the third, animated image of the next gallery is only an oversimplified dynamic representation of the longitudinal vibrations of the DNA intertwined helices which were found to be anharmonic rather than harmonic as often assumed in quantum dynamic simulations of DNA.

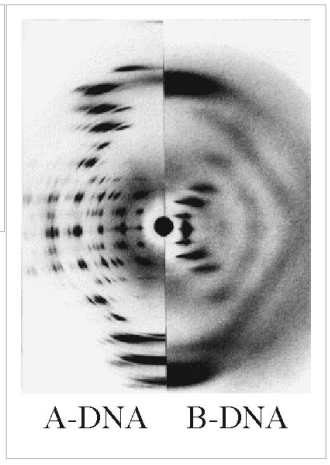


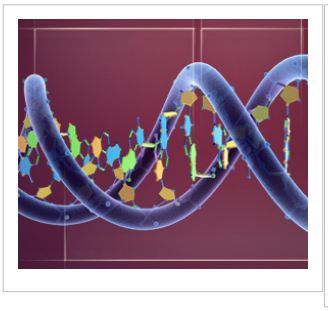


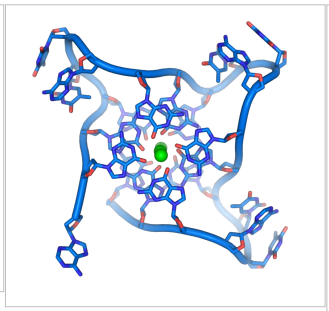


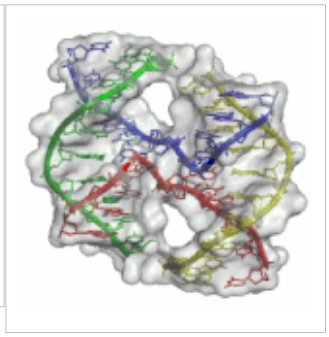










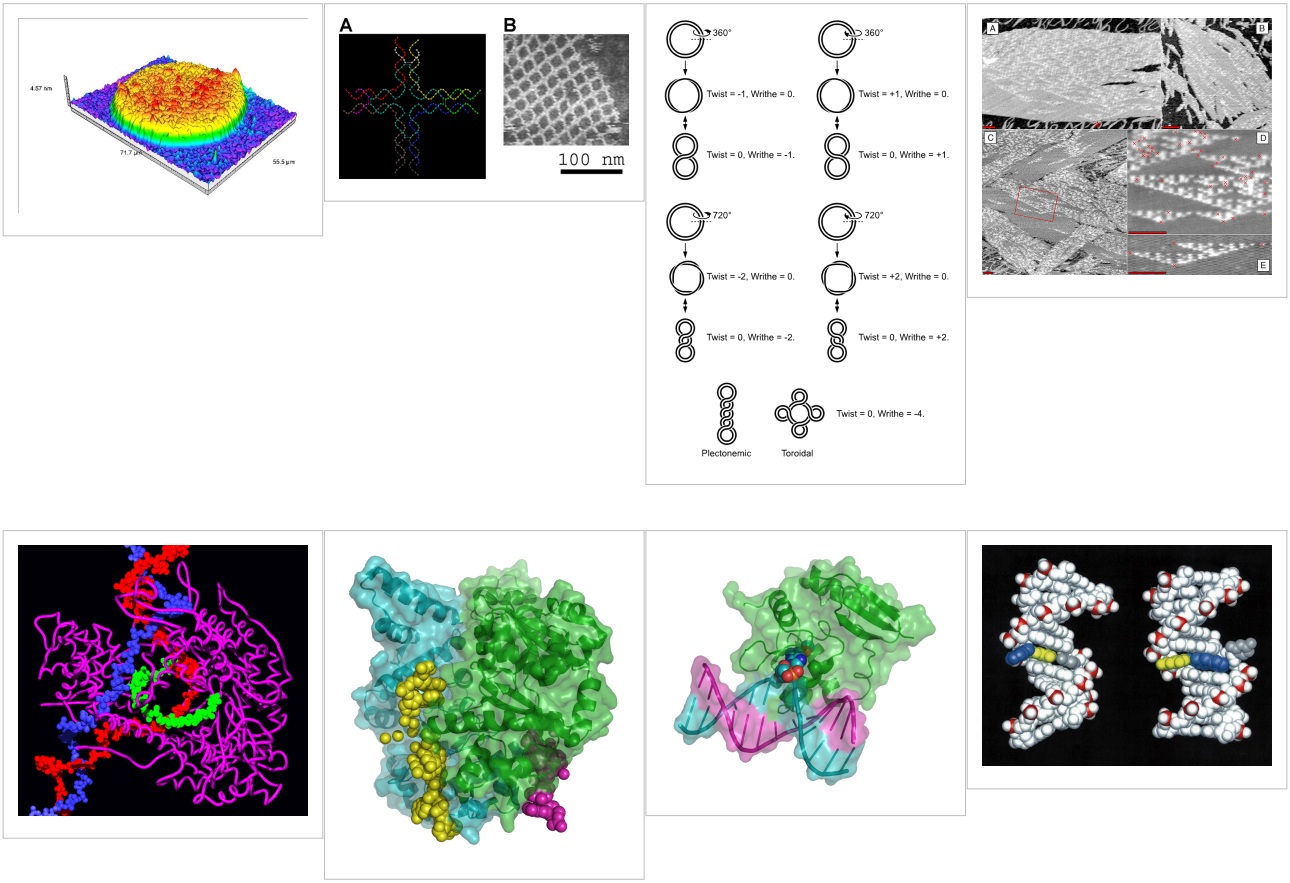


Human Genomics and Biotechnology Applications of DNA Molecular Modeling

The following two galleries of images illustrates various uses of DNA molecular modeling in Genomics and Biotechnology research applications from DNA repair to PCR and DNA nanostructures; each slide contains its own explanation and/or details. The first slide presents an overview of DNA applications, including DNA molecular models, with emphasis on Genomics and Biotechnology.

Applications of DNA molecular dynamics computations

- *First row* images present a DNA biochip and DNA nanostructures designed for DNA computing and other dynamic applications of DNA nanotechnology; last image in this row is of DNA arrays that display a representation of the Sierpinski gasket on their surfaces.
- *Second row*: the first two images show computer molecular models of RNA polymerase, followed by that of an E. coli, bacterial DNA primase template suggesting very complex dynamics at the interfaces between the enzymes and the DNA template; the fourth image illustrates in a computed molecular model the mutagenic, chemical interaction of a potent carcinogen molecule with DNA, and the last image shows the different interactions of specific fluorescence labels with DNA in human and orangoutan chromosomes.



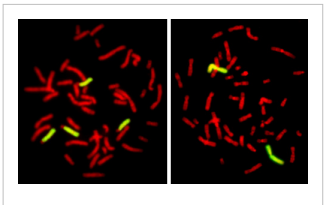
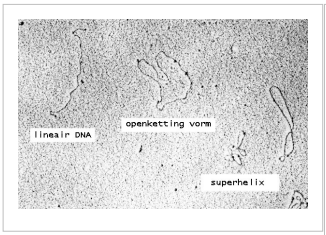
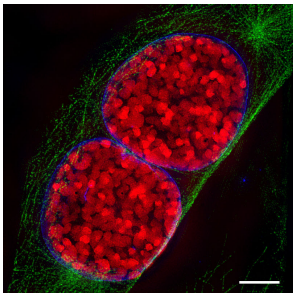
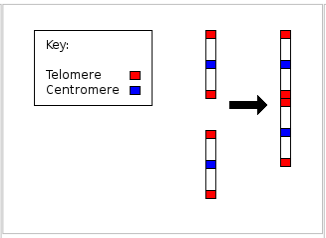


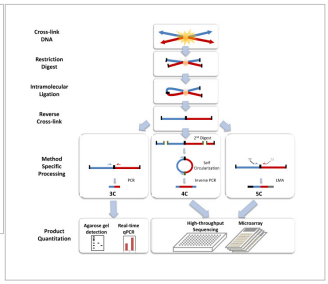
Image Gallery: *DNA Applications and Technologies at various scales in Biotechnology and Genomics research*

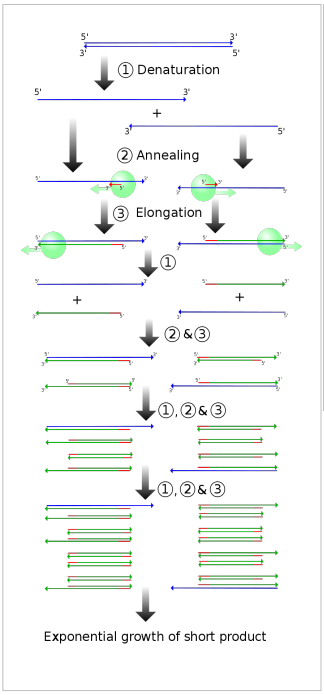
The first figure is an actual electron micrograph of a DNA fiber bundle, presumably of a single plasmid, bacterial DNA loop.

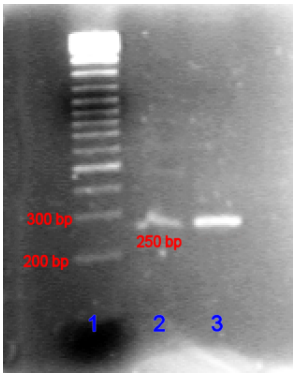


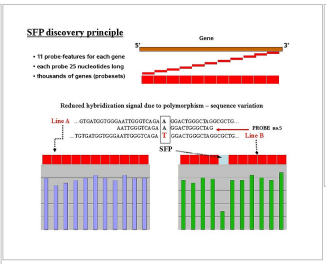


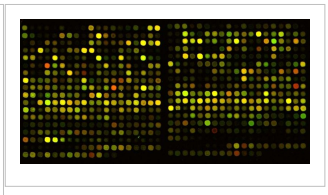


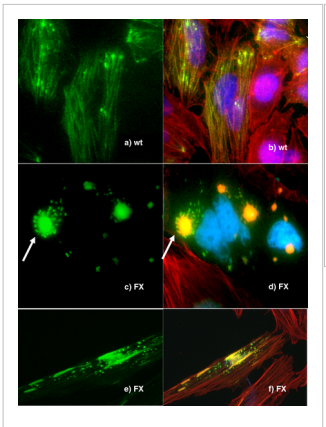


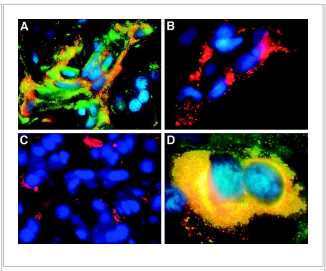


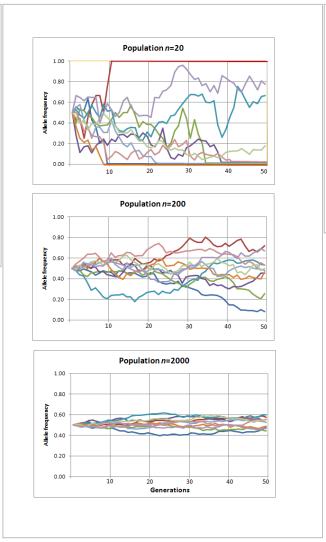


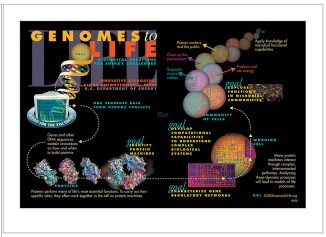










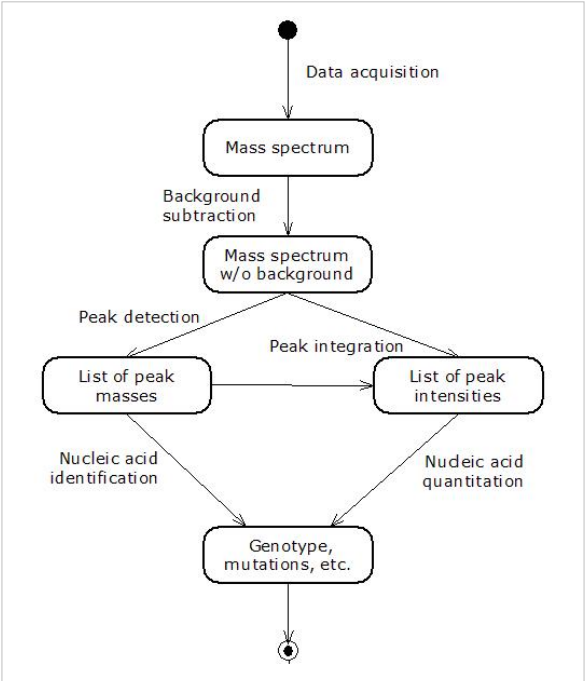


Databases for Genomics, DNA Dynamics and Sequencing

Genomic and structural databases

- CBS Genome Atlas Database [7] — contains examples of base skews.[60]
- The Z curve database of genomes — a 3-dimensional visualization and analysis tool of genomes [8][9] .
- DNA and other nucleic acids' molecular models: Coordinate files of nucleic acids molecular structure models in PDB and CIF formats [10]

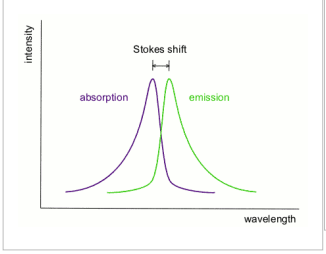
Mass spectrometry--Maldi informatics

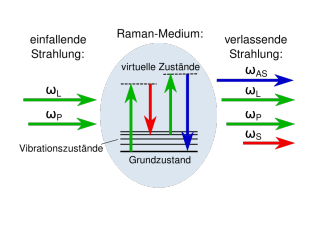


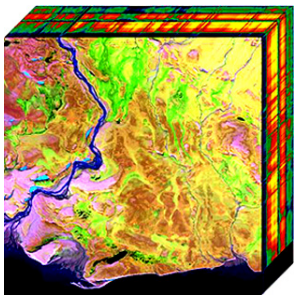
DNA Dynamics Data from Spectroscopy

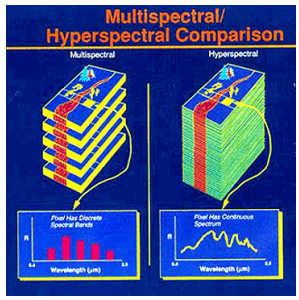
- FT-NMR[11] [12]
  - NMR Atlas--database [13]
  - mmcif downloadable coordinate files of nucleic acids in solution from 2D-FT NMR data [14]
  - NMR constraints files for NAs in PDB format [15]
- NMR microscopy[16]
- → Vibrational circular dichroism (VCD)
- Microwave spectroscopy
- FT-IR
- FT-NIR[17] [18] [19]
- Spectral, Hyperspectral, and → Chemical imaging)[20] [21] [22] [23] [24] [25] [26] .
- Raman spectroscopy/microscopy[27] and CARS[28] .
- Fluorescence correlation spectroscopy[29] [30] [31] [32] [33] [34] [35] [36] , Fluorescence cross-correlation spectroscopy and FRET[37] [38] [39] .
- Confocal microscopy[40]

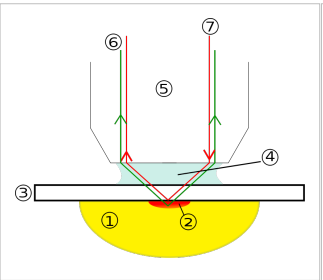
Gallery: CARS (Raman spectroscopy), Fluorescence confocal microscopy, and Hyperspectral imaging

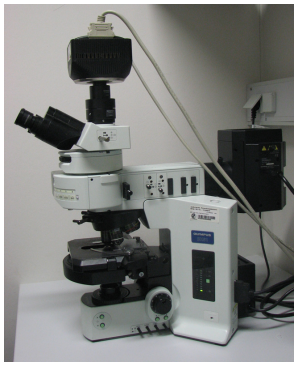


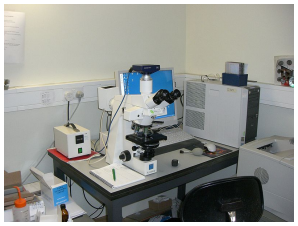


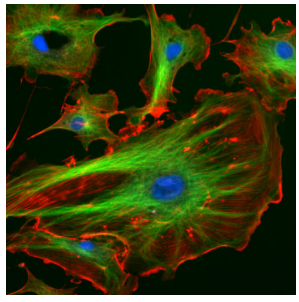


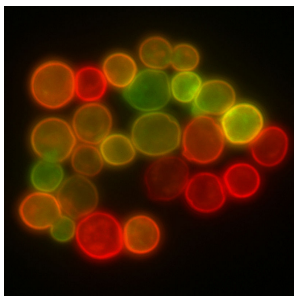
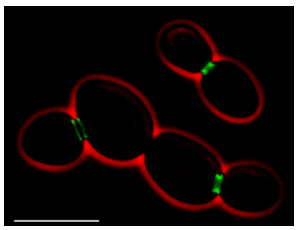
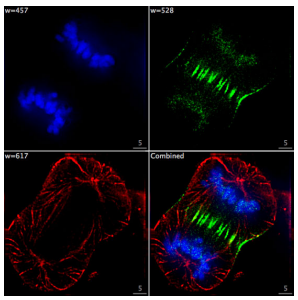


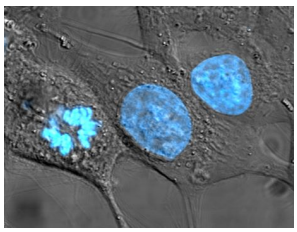
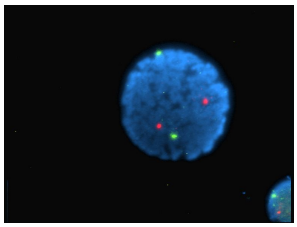
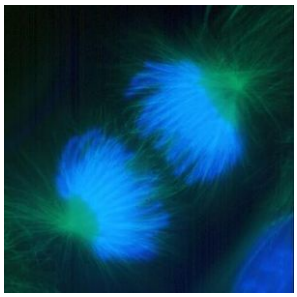
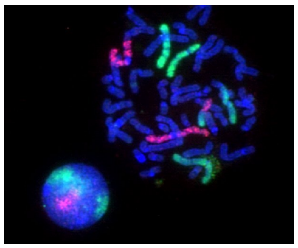
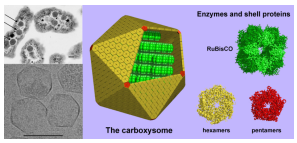








X-ray microscopy

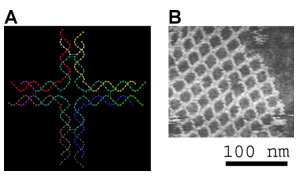
- Application of X-ray microscopy in the analysis of living hydrated cells [41]

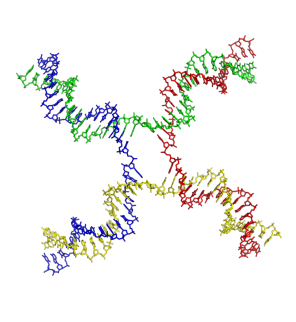
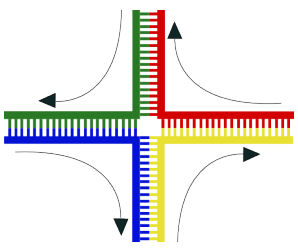
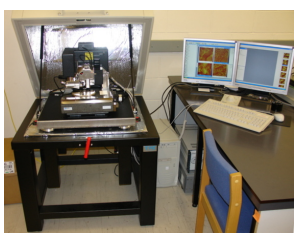
Atomic Force Microscopy (AFM)

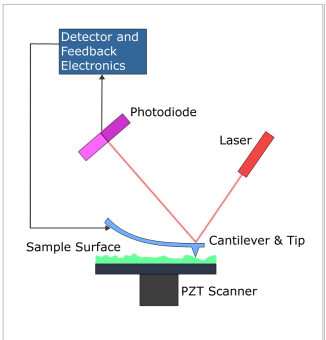
Two-dimensional DNA junction arrays have been visualized by Atomic Force Microscopy (AFM)[42] . Other imaging resources for AFM/Scanning probe microscopy(SPM) can be freely accessed at:

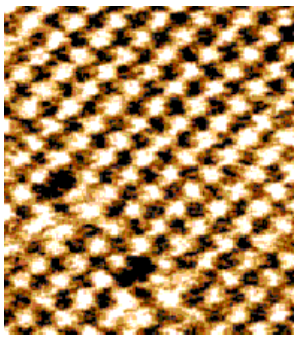
- How SPM Works [43]
- SPM Image Gallery - AFM STM SEM MFM NSOM and more. [44]

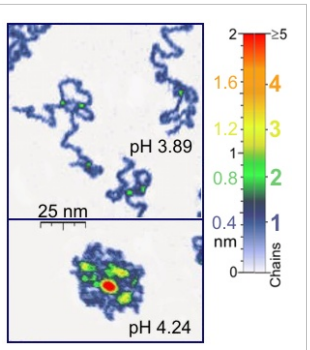
Gallery of AFM Images of DNA Nanostructures









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See also

- → DNA
- → Molecular modeling of DNA
- Molecular graphics
- Quantum computing
- MAYA-II
- DNA computing
- DNA structure
- Molecular structure
- → Molecular dynamics
- → Molecular topology
- DNA topology
- DNA, the Genome and Interactome
- Molecular structure
- Molecular geometry fluctuations
- Molecular interactions
- → Molecular topology
- Hydrogen bonding
- Hydrophobic interactions
- DNA dynamics and conformations
- DNA Conformational isomerism
- → 2D-FT NMRI and Spectroscopy
- → Paracrystalline lattices/Paracrystals
- NMR Spectroscopy
- → VCD or Vibrational circular dichroism
- Microwave spectroscopy
- Two-dimensional IR spectroscopy
- FRET and FCS- Fluorescence correlation spectroscopy
- Fluorescence cross-correlation spectroscopy (FCCS)
- Spectral imaging
- Hyperspectral imaging
- → Chemical imaging
- NMR microscopy
- X-ray scattering
- Neutron scattering

- Crystallography
- Crystal lattices
- Molecular geometry
- Nanostructure
- DNA nanotechnology
- Imaging
- Sirius visualization software
- Atomic force microscopy
- X-ray microscopy
- Liquid crystals
- Glasses
- QMC@Home
- Sir Lawrence Bragg, FRS
- Sir John Randall
- Francis Crick
- Manfred Eigen
- Felix Bloch
- Paul Lauterbur
- Maurice Wilkins
- Herbert Wilson, FRS
- Alex Stokes

External links

- DNA the Double Helix Game (http://nobelprize.org/educational_games/medicine/dna_double_helix/) From the official Nobel Prize web site
- MDDNA: Structural Bioinformatics of DNA (http://humphry.chem.wesleyan.edu:8080/MDDNA/)
- Double Helix 1953–2003 (http://www.ncbe.reading.ac.uk/DNA50/) National Centre for Biotechnology Education
- DNA under electron microscope (http://www.fidelitysystems.com/Unlinked_DNA.html)
- Ascalaph DNA (http://www.agilemolecule.com/Ascalaph/Ascalaph_DNA.html) — Commercial software for DNA modeling
- DNAlive: a web interface to compute DNA physical properties (http://mmb.pcb.ub.es/DNAlive). Also allows cross-linking of the results with the UCSC Genome browser and DNA dynamics.
- DiProDB: Dinucleotide Property Database (http://diprodb.fli-leibniz.de). The database is designed to collect and analyse thermodynamic, structural and other dinucleotide properties.
- Further details of mathematical and molecular analysis of DNA structure based on X-ray data (http://planetphysics.org/encyclopedia/BesselFunctionsApplicationsToDiffractionByHelicalStructures.html)
- Bessel functions corresponding to Fourier transforms of atomic or molecular helices. (http://planetphysics.org/?op=getobj&from=objects&name=BesselFunctionsAndTheirApplicationsToDiffractionByHelicalStructures)
- Application of X-ray microscopy in analysis of living hydrated cells (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12379938)

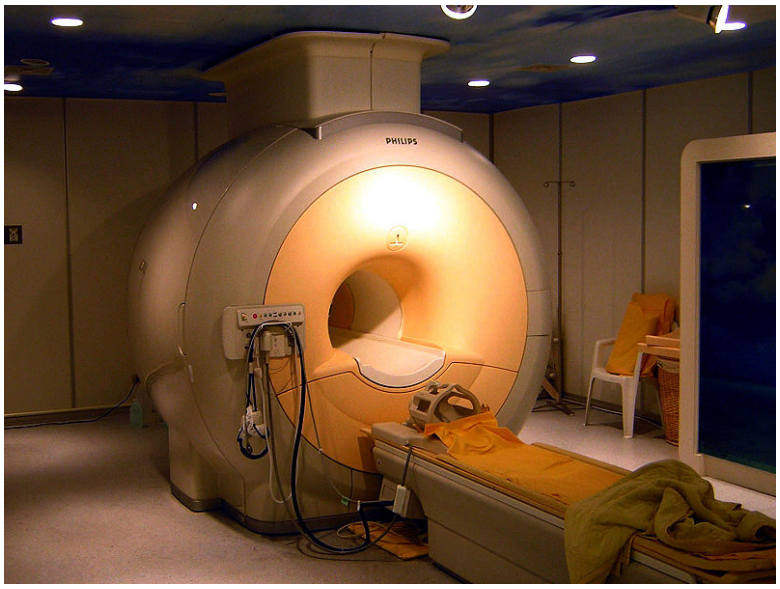
- Characterization in nanotechnology some pdfs (http://nanocharacterization.sitesled.com/)
- An overview of STM/AFM/SNOM principles with educative videos (http://www.ntmdt.ru/SPM-Techniques/Principles/)
- SPM Image Gallery - AFM STM SEM MFM NSOM and More (http://www.rhk-tech.com/results/showcase.php)
- How SPM Works (http://www.parkafm.com/New_html/resources/01general.php)
- U.S. National DNA Day (http://www.genome.gov/10506367) — watch videos and participate in real-time discusssions with scientists.
- The Secret Life of DNA - DNA Music compositions (http://www.tjmitchell.com/stuart/dna.html)

2D-FT NMRI and Spectroscopy

2D-FT Nuclear magnetic resonance imaging (**2D-FT NMRI**), or **Two-dimensional Fourier transform** nuclear magnetic resonance imaging (**NMRI**), is primarily a non—invasive imaging technique most commonly used in biomedical research and medical radiology/nuclear medicine/MRI to visualize structures and functions of the living systems and single cells. For example it can provides fairly detailed images of a human body in any selected cross-sectional plane, such as longitudinal, transversal, sagital, etc. The basic NMR phenomenon or physical principle[1] is essentially the same in N(MRI), nuclear magnetic resonance/FT (NMR) spectroscopy, topical NMR, or even in Electron Spin Resonance /EPR; however, the details are significantly different at present for EPR, as only in the early days of NMR the static magnetic field was scanned for obtaining spectra, as it is still the case in many EPR or ESR spectrometers. NMRI, on the other hand, often utilizes a linear magnetic field gradient to obtain an image that combines the visualization of molecular structure and dynamics. It is this dynamic aspect of NMRI, as well as its highest sensitivity for the ^{1}H nucleus that distinguishes it very dramatically from X-ray CAT scanning that 'misses' hydrogens because of their very low X-ray scattering factor.

Thus, NMRI provides much greater contrast especially for the different soft tissues of the body than computed tomography (CT) as its most sensitive option observes the nuclear spin distribution and dynamics of highly mobile molecules that contain the naturally abundant, stable hydrogen isotope ^{1}H as in plasma water molecules, blood, disolved metabolites and fats. This approach makes it most useful in cardiovascular, oncological (cancer), neurological (brain), musculoskeletal, and cartilage imaging. Unlike CT, it uses no ionizing radiation, and also unlike nuclear imaging it does not employ any radioactive isotopes. Some of the first MRI images reported were published in 1973[2] and the first study performed on a human took place on July 3, 1977.[3] Earlier papers were also published by Sir Peter Mansfield[4] in UK (Nobel Laureate in 2003), and R. Damadian in the USA[5] , (together with an approved patent for 'fonar', or magnetic imaging). The detailed physical theory of NMRI was published by Peter Mansfield in 1973[6] . Unpublished 'high-resolution' (50 micron resolution) images of other living systems, such as hydrated wheat grains, were also obtained and communicated in UK in 1977-1979, and were subsequently confirmed by articles published in *Nature* by Peter Callaghan.

NMR Principle



Advanced 4.7 T clinical diagnostics and biomedical research NMR Imaging instrument.

Certain nuclei such as ^{1}H nuclei, or `fermions' have spin-1/2, because there are two spin states, referred to as "up" and "down" states. The nuclear magnetic resonance absorption phenomenon occurs when samples containing such nuclear spins are placed in a static magnetic field and a very short radiofrequency pulse is applied with a center, or carrier, frequency matching that of the transition between the up and down states of the spin-1/2 ^{1}H nuclei that were polarized by the static magnetic field. [7] Very low field schemes have also been recently reported.[8]

Chemical Shifts

NMR is a very useful family of techniques for chemical and biochemical research because of the chemical shift; this effect consists in a frequency shift of the nuclear magnetic resonance for specific chemical groups or atoms as a result of the partial shielding of the corresponding nuclei from the applied, static external magnetic field by the electron orbitals (or molecular orbitals) surrounding such nuclei present in the chemical groups. Thus, the higher the electron density surrounding a specific nucleus the larger the chemical shift will be. The resulting magnetic field at the nucleus is thus lower than the applied external magnetic field and the resonance frequencies observed as a result of such shielding are lower than the value that would be observed in the absence of any electronic orbital shielding. Furthermore, in order to obtain a chemical shift value independent of the strength of the applied magnetic field and allow for the direct comparison of spectra obtained at different magnetic field values, the chemical shift is defined by the ratio of the strength of the local magnetic field value at the observed (electron orbital-shielded) nucleus by the external magnetic field strength, $\mathbf{H}_{loc}/\ \mathbf{H}_{0}$. The first NMR observations of the chemical shift, with the correct physical chemistry interpretation, were reported for ^{19}F containing compounds in the early 1950s by Herbert S. Gutowsky and Charles P. Slichter from the University of Illinois at Urbana (USA).

A related effect in metals is called the Knight shift, which is due only to the conduction electrons. Such conduction electrons present in metals induce an "additional" local field at the nuclear site, due to the spin re-orientation of the conduction electrons in the presence of the applied (constant), external magnetic field. This is only broadly `similar' to the chemical shift in either solutions or diamagnetic solids.

NMR Imaging Principles

A number of methods have been devised for combining magnetic field gradients and radiofrequency pulsed excitation to obtain an image. Two major maethods involve either 2D -FT or 3D-FT[9] reconstruction from projections, somewhat similar to Computed Tomography, with the exception of the image interpretation that in the former case must include dynamic and relaxation/contrast enhancement information as well. Other schemes involve building the NMR image either point-by-point or line-by-line. Some schemes use instead gradients in the rf field rather than in the static magnetic field. The majority of NMR images routinely obtained are either by the Two-Dimensional Fourier Transform (2D-FT) technique [10] (with slice selection), or by the Three-Dimensional Fourier Transform (3D—FT) techniques that are however much more time consuming at present. 2D-FT NMRI is sometime called in common parlance a "spin-warp". An NMR image corresponds to a spectrum consisting of a number of `spatial frequencies' at different locations in the sample investigated, or in a patient.[11] A two–dimensional Fourier transformation of such a "real" image may be considered as a representation of such "real waves" by a matrix of spatial frequencies known as the k–space. We shall see next in some mathematical detail how the 2D-FT computation works to obtain 2D-FT NMR images.

Two-dimensional Fourier transform imaging and spectroscopy

A two-dimensional Fourier transform (2D-FT) is computed numerically or carried out in two stages, both involving `standard', one-dimensional Fourier transforms. However, the second stage Fourier transform is not the inverse Fourier transform (which would result in the original function that was transformed at the first stage), but a Fourier transform in a second variable—which is `shifted' in value—relative to that involved in the result of the first Fourier transform. Such 2D-FT analysis is a very powerful method for both NMRI and two-dimensional nuclear magnetic resonance spectroscopy (2D-FT NMRS)[12] that allows the three-dimensional reconstruction of polymer and biopolymer structures at atomic resolution.[13] for molecular weights (Mw) of dissolved biopolymers in aqueous solutions (for example) up to about 50,000 Mw. For larger biopolymers or polymers, more complex methods have been developed to obtain limited structural resolution needed for partial 3D-reconstructions of higher molecular structures, e.g. for up 900,000 Mw or even oriented microcrystals in aqueous suspensions or single crystals; such methods have also been reported for *in vivo* 2D-FT NMR spectroscopic studies of algae, bacteria, yeast and certain mammalian cells, including human ones. The 2D-FT method is also widely utilized in optical spectroscopy, such as *2D-FT NIR hyperspectral imaging* (2D-FT NIR-HS), or in MRI imaging for research and clinical, diagnostic applications in Medicine. In the latter case, 2D-FT NIR-HS has recently allowed the identification of single, malignant cancer cells surrounded by healthy human breast tissue at about 1 micron resolution, well-beyond the resolution obtainable by 2D-FT NMRI for such systems in the limited time available for such diagnostic investigations (and also in magnetic fields up to the FDA approved magnetic field strength $\mathbf{H}_0$ of 4.7 T, as shown in the top image of the state-of-the-art NMRI instrument). A more precise mathematical definition of the `double' (2D) Fourier transform involved in both 2D NMRI and 2D-FT NMRS is specified next, and a precise example follows this generally accepted definition.

2D-FT Definition

A *2D-FT, or two-dimensional Fourier transform*, is a standard Fourier transformation of a function of two variables, **f**(x_1, x_2), carried first in the first variable x_1, followed by the Fourier transform in the second variable x_2 of the resulting function **F**(s_1,x_2). Note that in the case of both 2D-FT NMRI and 2D-FT NMRS the two independent variables in this definition are in the time domain, whereas the results of the two successive Fourier transforms have, of course, frequencies as the independent variable in the NMRS, and ultimately spatial coordinates for both 2D NMRI and 2D-FT NMRS following computer structural recontructions based on special algorithms that are different from FT or 2D-FT. Moreover, such structural algorithms are different for 2D NMRI and 2D-FT NMRS: in the former case they involve macroscopic, or anatomical structure detrmination, whereas in the latter case of 2D-FT NMRS the atomic structure reconstruction algorithms are based on the quantum theory of a microphysical (quantum) process such as nuclear Overhauser enhancement NOE, or specific magnetic dipole-dipole interactions[14] between neighbor nuclei.

Example 1

A 2D Fourier transformation and phase correction is applied to a set of 2D NMR (FID) signals: **s**(t_1,t_2) yielding a real 2D-FT NMR `spectrum' (collection of 1D FT-NMR spectra) represented by a matrix **S** whose elements are

$$\mathbf{S}\ (\nu_1, \nu_2) = \mathbf{Re} \int \int cos(\nu_1 t_1) exp^{(-i\nu_2 t_2)} s(t_1, t_2) dt_1 dt_2$$

where : ν_1 and : ν_2 denote the discrete indirect double-quantum and single-quantum(detection) axes, respectively, in the 2D NMR experiments. Next, the *covariance matrix* is calculated in the frequency domain according to the following equation

C $(\nu_2', \nu_2) = S^T S = \sum_{\nu^1} [S(\nu_1, \nu_2') S(\nu_1, \nu_2)],$ with : ν_2, ν_2' taking all possible single-quantum frequency values and with the summation carried out over all discrete, double quantum frequencies : ν_1.

Example 2

Atomic Structure from 2D-FT STEM Images [15] of electron distributions in a high-temperature cuprate superconductor `paracrystal' reveal both the domains (or `location') and the local symmetry of the 'pseudo-gap' in the electron-pair correlation band responsible for the high—temperature superconductivity effect (obtained at Cornell University). So far there have been three Nobel prizes awarded for 2D-FT NMR/MRI during 1992-2003, and an additional, earlier Nobel prize for 2D-FT of X-ray data (`CAT scans'); recently the advanced possibilities of 2D-FT techniques in Chemistry, Physiology and Medicine [16] received very significant recognition.[17]

Brief explanation of NMRI diagnostic uses in Pathology

As an example, a diseased tissue such as a malign tumor, can be detected by 2D-FT NMRI because the hydrogen nuclei of molecules in different tissues return to their equilibrium spin state at different relaxation rates, and also because of the manner in which a malign tumor spreads and grows rapidly along the blood vessels adjacent to the tumor, also inducing further vascularization to occur. By changing the pulse delays in the RF pulse

sequence employed, and/or the RF pulse sequence itself, one may obtain a `relaxation—based contrast', or contrast enhancement between different types of body tissue, such as normal vs. diseased tissue cells for example. Excluded from such diagnostic observations by NMRI are all patients with ferromagnetic metal implants, (e.g., cochlear implants), and all cardiac pacemaker patients who cannot undergo any NMRI scan because of the very intense magnetic and RF fields employed in NMRI which would strongly interfere with the correct functioning of such pacemakers. It is, however, conceivable that future developments may also include along with the NMRI diagnostic treatments with special techniques involving applied magnetic fields and very high frequency RF. Already, surgery with special tools is being experimented on in the presence of NMR imaging of subjects.Thus, NMRI is used to image almost every part of the body, and is especially useful for diagnosis in neurological conditions, disorders of the muscles and joints, for evaluating tumors, such as in lung or skin cancers, abnormalities in the heart (especially in children with hereditary disorders), blood vessels, CAD, atherosclerosis and cardiac infarcts [18] (courtesy of Dr. Robert R. Edelman)

See also

- Nuclear magnetic resonance (NMR)
- Edward Mills Purcell
- Felix Bloch
- Medical imaging
- Paul C. Lauterbur
- Magnetic resonance microscopy
- Peter Mansfield
- Computed tomography (CT)
- Solid-state NMR
- Knight shift
- John Hasbrouck Van Vleck
- Chemical shift
- Herbert S. Gutowsky
- John S. Waugh
- Charles Pence Slichter
- Protein nuclear magnetic resonance spectroscopy
- Kurt Wüthrich
- Nuclear Overhauser effect
- Fourier transform spectroscopy(FTS)
- Jean Jeneer
- Richard R. Ernst
- FT-NIRS (NIR)
- Magnetic resonance elastography
- Relaxation
- Earth's field NMR (EFNMR)
- Robinson oscillator

Footnotes

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External links

- Cardiac Infarct or "heart attack" Imaged in Real Time by 2D-FT NMRI (http://www.mr-tip.com/exam_gifs/cardiac_infarct_short_axis_cine_6.gif)
- Interactive Flash Animation on MRI (http://www.e-mri.org) - *Online Magnetic Resonance Imaging physics and technique course*
- Herbert S. Gutowsky
- Jiri Jonas and Charles P. Slichter: NMR Memoires at NAS about Herbert Sander Gutowsky; NAS = National Academy of Sciences, USA, (http://books.nap.edu/html/biomems/hgutowsky.pdf)
- 3D Animation Movie about MRI Exam (http://www.patiencys.com/MRI/)
- International Society for Magnetic Resonance in Medicine (http://www.ismrm.org)
- Danger of objects flying into the scanner (http://www.simplyphysics.com/flying_objects.html)

Related Wikipedia websites

- Medical imaging
- Computed tomography
- Magnetic resonance microscopy
- Fourier transform spectroscopy
- FT-NIRS
- Magnetic resonance elastography
- Nuclear magnetic resonance (NMR)
- Chemical shift
- Relaxation
- Robinson oscillator
- Earth's field NMR (EFNMR)
- Rabi cycle

Chemical imaging

Chemical imaging is the simultaneous measurement of spectra (chemical information) and images or pictures (spatial information)[1] [2] The technique is most often applied to either solid or gel samples, and has applications in chemistry, biology[3] [4] [5] [6] [7] [8] , medicine[9] [10] , pharmacy[11] (see also for example: Chemical Imaging Without Dyeing [12]), food science, biotechnology[13] [14] , agriculture and industry (see for example:NIR Chemical Imaging in Pharmaceutical Industry [15] and Pharmaceutical Process Analytical Technology: [16]). NIR, IR and Raman chemical imaging is also referred to as hyperspectral, spectroscopic, spectral or multispectral imaging (also see microspectroscopy). However, other ultra-sensitive and selective, chemical imaging techniques are also in use that involve either UV-visible or fluorescence microspectroscopy. Chemical imaging techniques can be used to analyze samples of all sizes, from the single molecule[17] [18] to the cellular level in biology and medicine[19] [20] [21] , and to images of planetary systems in astronomy, but different instrumentation is employed for making observations on such widely different systems.

Chemical imaging instrumentation is composed of three components: a radiation source to illuminate the sample, a spectrally selective element, and usually a detector array (the camera) to collect the images. When many stacked spectral channels (wavelengths) are collected for different locations of the microspectrometer focus on a line or planar array in the focal plane, the data is called hyperspectral; fewer wavelength data sets are called multispectral. The data format is called a hypercube. The data set may be visualized as a three-dimensional block of data spanning two spatial dimensions (x and y), with a series of wavelengths (lambda) making up the third (spectral) axis. The hypercube can be visually and mathematically treated as a series of spectrally resolved images (each image plane corresponding to the image at one wavelength) or a series of spatially resolved spectra. The analyst may choose to view the spectrum measured at a particular spatial location; this is useful for chemical identification. Alternatively, selecting an image plane at a particular wavelength can highlight the spatial distribution of sample components, provided that their spectral signatures are different at the selected wavelength.

Many materials, both manufactured and naturally occurring, derive their functionality from the spatial distribution of sample components. For example, extended release pharmaceutical formulations can be achieved by using a coating that acts as a barrier layer. The release of active ingredient is controlled by the presence of this barrier, and imperfections in the coating, such as discontinuities, may result in altered performance. In the semi-conductor industry, irregularities or contaminants in silicon wafers or printed micro-circuits can lead to failure of these components. The functionality of biological systems is also dependent upon chemical gradients – a single cell, tissue, and even whole organs function because of the very specific arrangement of components. It has been shown that even small changes in chemical composition and distribution may be an early indicator of disease.

Any material that depends on chemical gradients for functionality may be amenable to study by an analytical technique that couples spatial and chemical characterization. To efficiently and effectively design and manufacture such materials, the ‘what’ and the ‘where’ must both be measured. The demand for this type of analysis is increasing as manufactured materials become more complex. Chemical imaging techniques not only

permit visualization of the spatially resolved chemical information that is critical to understanding modern manufactured products, but it is also a non-destructive technique so that samples are preserved for further testing.

History

Commercially available laboratory-based chemical imaging systems emerged in the early 1990s (ref. 1-5). In addition to economic factors, such as the need for sophisticated electronics and extremely high-end computers, a significant barrier to commercialization of infrared imaging was that the focal plane array (FPA) needed to read IR images were not readily available as commercial items. As high-speed electronics and sophisticated computers became more commonplace, and infrared cameras became readily commercially available, laboratory chemical imaging systems were introduced.

Initially used for novel research in specialized laboratories, chemical imaging became a more commonplace analytical technique used for general R&D, quality assurance (QA) and quality control (QC) in less than a decade. The rapid acceptance of the technology in a variety of industries (pharmaceutical, polymers, semiconductors, security, forensics and agriculture) rests in the wealth of information characterizing both chemical composition and morphology. The parallel nature of chemical imaging data makes it possible to analyze multiple samples simultaneously for applications that require high throughput analysis in addition to characterizing a single sample.

Principles

Chemical imaging shares the fundamentals of vibrational spectroscopic techniques, but provides additional information by way of the simultaneous acquisition of spatially resolved spectra. It combines the advantages of digital imaging with the attributes of spectroscopic measurements. Briefly, vibrational spectroscopy measures the interaction of light with matter. Photons that interact with a sample are either absorbed or scattered; photons of specific energy are absorbed, and the pattern of absorption provides information, or a fingerprint, on the molecules that are present in the sample.

On the other hand, in terms of the observation setup, chemical imaging can be carried out in one of the following modes: (optical) absorption, emission (fluorescence), (optical) transmission or scattering (Raman). A consensus currently exists that the fluorescence (emission) and Raman scattering modes are the most sensitive and powerful, but also the most expensive.

In a transmission measurement, the radiation goes through a sample and is measured by a detector placed on the far side of the sample. The energy transferred from the incoming radiation to the molecule(s) can be calculated as the difference between the quantity of photons that were emitted by the source and the quantity that is measured by the detector. In a diffuse reflectance measurement, the same energy difference measurement is made, but the source and detector are located on the same side of the sample, and the photons that are measured have re-emerged from the illuminated side of the sample rather than passed through it. The energy may be measured at one or multiple wavelengths; when a series of measurements are made, the response curve is called a spectrum.

A key element in acquiring spectra is that the radiation must somehow be energy selected – either before or after interacting with the sample. Wavelength selection can be

accomplished with a fixed filter, tunable filter, spectrograph, an interferometer, or other devices. For a fixed filter approach, it is not efficient to collect a significant number of wavelengths, and multispectral data are usually collected. Interferometer-based chemical imaging requires that entire spectral ranges be collected, and therefore results in hyperspectral data. Tunable filters have the flexibility to provide either multi- or hyperspectral data, depending on analytical requirements.

Spectra may be measured one point at a time using a single element detector (single-point mapping), as a line-image using a linear array detector (typically 16 to 28 pixels) (linear array mapping), or as a two-dimensional image using a Focal Plane Array (FPA)(typically 256 to 16,384 pixels) (FPA imaging). For single-point the sample is moved in the x and y directions point-by-point using a computer-controlled stage. With linear array mapping, the sample is moved line-by-line with a computer-controlled stage. FPA imaging data are collected with a two-dimensional FPA detector, hence capturing the full desired field-of-view at one time for each individual wavelength, without having to move the sample. FPA imaging, with its ability to collected tens of thousands of spectra simultaneously is orders of magnitude faster than linear arrays which are can typically collect 16 to 28 spectra simultaneously, which are in turn much faster than single-point mapping.

Terminology

Some words common in spectroscopy, optical microscopy and photography have been adapted or their scope modified for their use in chemical imaging. They include: resolution, field of view and magnification. There are two types of resolution in chemical imaging. The spectral resolution refers to the ability to resolve small energy differences; it applies to the spectral axis. The spatial resolution is the minimum distance between two objects that is required for them to be detected as distinct objects. The spatial resolution is influenced by the field of view, a physical measure of the size of the area probed by the analysis. In imaging, the field of view is a product of the magnification and the number of pixels in the detector array. The magnification is a ratio of the physical area of the detector array divided by the area of the sample field of view. Higher magnifications for the same detector image a smaller area of the sample.

Types of vibrational chemical imaging instruments

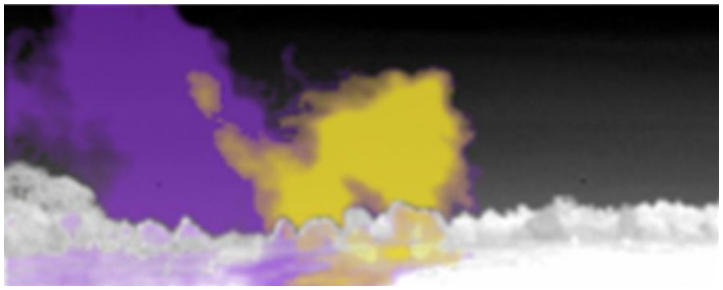
Chemical imaging has been implemented for mid-infrared, near-infrared spectroscopy and Raman spectroscopy. As with their bulk spectroscopy counterparts, each imaging technique has particular strengths and weaknesses, and are best suited to fulfill different needs.

Mid-infrared chemical imaging

Mid-infrared (MIR) spectroscopy probes fundamental molecular vibrations, which arise in the spectral range 2,500-25,000 nm. Commercial imaging implementations in the MIR region typically employ Fourier Transform Infrared (FT-IR) interferometers and the range is more commonly presented in wavenumber, 4,000 – 400 cm^{-1}. The MIR absorption bands tend to be relatively narrow and well-resolved; direct spectral interpretation is often possible by an experienced spectroscopist. MIR spectroscopy can distinguish subtle changes in chemistry and structure, and is often used for the identification of unknown materials. The absorptions in this spectral range are relatively strong; for this reason, sample presentation is important to limit the amount of material interacting with the

incoming radiation in the MIR region. Most data collected in this range is collected in transmission mode through thin sections (~10 micrometres) of material. Water is a very strong absorber of MIR radiation and wet samples often require advanced sampling procedures (such as attenuated total reflectance). Commercial instruments include point and line mapping, and imaging. All employ an FT-IR interferometer as wavelength selective element and light source.

For types of MIR microscope, see Microscopy#infrared microscopy.



Remote chemical imaging of a simultaneous release of SF_6 and NH_3 at 1.5km using the FIRST imaging spectrometer[22]

Atmospheric windows in the infrared spectrum are also employed to perform chemical imaging remotely. In these spectral regions the atmospheric gases (mainly water and CO_2) present low absorption and allow infrared viewing over kilometer distances. Target molecules can then be viewed using the selective absorption/emission processes described above. An example of the chemical imaging of a simultaneous release of SF_6 and NH_3 is shown in the image.

Near-infrared chemical imaging

The analytical near infrared (NIR) region spans the range from approximately 700-2,500 nm. The absorption bands seen in this spectral range arise from overtones and combination bands of O-H, N-H, C-H and S-H stretching and bending vibrations. Absorption is one to two orders of magnitude smaller in the NIR compared to the MIR; this phenomenon eliminates the need for extensive sample preparation. Thick and thin samples can be analyzed without any sample preparation, it is possible to acquire NIR chemical images through some packaging materials, and the technique can be used to examine hydrated samples, within limits. Intact samples can be imaged in transmittance or diffuse reflectance.

The lineshapes for overtone and combination bands tend to be much broader and more overlapped than for the fundamental bands seen in the MIR. Often, multivariate methods are used to separate spectral signatures of sample components. NIR chemical imaging is particularly useful for performing rapid, reproducible and non-destructive analyses of known materials[23] [24] . NIR imaging instruments are typically based on one of two platforms: imaging using a tunable filter and broad band illumination, and line mapping employing an FT-IR interferometer as the wavelength filter and light source.

Raman chemical imaging

The Raman shift chemical imaging spectral range spans from approximately 50 to 4,000 cm^{-1}; the actual spectral range over which a particular Raman measurement is made is a function of the laser excitation frequency. The basic principle behind Raman spectroscopy differs from the MIR and NIR in that the x-axis of the Raman spectrum is measured as a function of energy shift (in cm^{-1}) relative to the frequency of the laser used as the source of radiation. Briefly, the Raman spectrum arises from inelastic scattering of incident photons, which requires a change in polarizability with vibration, as opposed to infrared absorption, which requires a change in dipole moment with vibration. The end result is spectral

information that is similar and in many cases complementary to the MIR. The Raman effect is weak - only about one in 10^7 photons incident to the sample undergoes Raman scattering. Both organic and inorganic materials possess a Raman spectrum; they generally produce sharp bands that are chemically specific. Fluorescence is a competing phenomenon and, depending on the sample, can overwhelm the Raman signal, for both bulk spectroscopy and imaging implementations.

Raman chemical imaging requires little or no sample preparation. However, physical sample sectioning may be used to expose the surface of interest, with care taken to obtain a surface that is as flat as possible. The conditions required for a particular measurement dictate the level of invasiveness of the technique, and samples that are sensitive to high power laser radiation may be damaged during analysis. It is relatively insensitive to the presence of water in the sample and is therefore useful for imaging samples that contain water such as biological material.

Fluorescence imaging (visible and NIR)

This emission microspectroscopy mode is the most sensitive in both visible and FT-NIR microspectroscopy, and has therefore numerous biomedical, biotechnological and agricultural applications. There are several powerful, highly specific and sensitive fluorescence techniques that are currently in use, or still being developed; among the former are FLIM, FRAP, FRET and FLIM-FRET; among the latter are NIR fluorescence and probe-sensitivity enhanced NIR fluorescence microspectroscopy and nanospectroscopy techniques (see "Further reading" section).

Sampling and samples

The value of imaging lies in the ability to resolve spatial heterogeneities in solid-state or gel/gel-like samples. Imaging a liquid or even a suspension has limited use as constant sample motion serves to average spatial information, unless ultra-fast recording techniques are employed as in fluorescence correlation microspectroscopy or FLIM obsevations where a single molecule may be monitored at extremely high (photon) detection speed. High-throughput experiments (such as imaging multi-well plates) of liquid samples can however provide valuable information. In this case, the parallel acquisition of thousands of spectra can be used to compare differences between samples, rather than the more common implementation of exploring spatial heterogeneity within a single sample.

Similarly, there is no benefit in imaging a truly homogeneous sample, as a single point spectrometer will generate the same spectral information. Of course the definition of homogeneity is dependent on the spatial resolution of the imaging system employed. For MIR imaging, where wavelengths span from 3-10 micrometres, objects on the order of 5 micrometres may theoretically be resolved. The sampled areas are limited by current experimental implementations because illumination is provided by the interferometer. Raman imaging may be able to resolve particles less than 1 micrometre in size, but the sample area that can be illuminated is severely limited. With Raman imaging, it is considered impractical to image large areas and, consequently, large samples. FT-NIR chemical/hyperspectral imaging usually resolves only larger objects (>10 micrometres), and is better suited for large samples because illumination sources are readily available. However, FT-NIR microspectroscopy was recently reported to be capable of about 1.2 micron (micrometer) resolution in biological samples[25] Furthermore, two-photon

excitation FCS experiments were reported to have attained 15 nanometer resolution on biomembrane thin films with a special coincidence photon-counting setup.

Detection limit

The concept of the detection limit for chemical imaging is quite different than for bulk spectroscopy, as it depends on the sample itself. Because a bulk spectrum represents an average of the materials present, the spectral signatures of trace components are simply overwhelmed by dilution. In imaging however, each pixel has a corresponding spectrum. If the physical size of the trace contaminant is on the order of the pixel size imaged on the sample, its spectral signature will likely be detectable. If however, the trace component is dispersed homogeneously (relative to pixel image size) throughout a sample, it will not be detectable. Therefore, detection limits of chemical imaging techniques are strongly influenced by particle size, the chemical and spatial heterogeneity of the sample, and the spatial resolution of the image.

Data analysis

Data analysis methods for chemical imaging data sets typically employ mathematical algorithms common to single point spectroscopy or to image analysis. The reasoning is that the spectrum acquired by each detector is equivalent to a single point spectrum; therefore pre-processing, chemometrics and pattern recognition techniques are utilized with the similar goal to separate chemical and physical effects and perform a qualitative or quantitative characterization of individual sample components. In the spatial dimension, each chemical image is equivalent to a digital image and standard image analysis and robust statistical analysis can be used for feature extraction.

See also

- Multispectral image
- Microspectroscopy
- Imaging spectroscopy

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